Available online at www.sciencedirect.com
SCIENCE DIRECT®
PHYTOCHEMISTRY
Phytochemistry 66 (2005) 2012–2031
www.elsevier.com/locate/phytochem

Review

Systematics and health effects of chemically distinct tannins in medicinal plants ☆

Takuo Okuda *,[1]

Okayama University, Tsushima, Okayama 700-8530, Japan

Received 23 August 2004; received in revised form 20 December 2004
Available online 27 June 2005

Abstract

The research began with an investigation of tannins from traditional medicinal plants and resulted in isolation and structure determination of hundreds of ellagitannins and dehydroellagitannins, as well as their oligomers and oxidized derivatives with various structures specific to each plant species. These polyphenols have been classified according to the stage of oxidative structural transformation and oligomerization, into types I–IV and I+ to IV+, etc. Parallels were found between their oxidative transformations and plant evolution. They were also classified by the linkage units between the monomers, into DOG, GOD, GOG and DOGOD types (D = *D*iphenoyl, G = *G*alloyl, O = *O*xygen), etc. Besides their fundamental activities, e.g., reduction and anti-peroxidation properties, remarkable biological and pharmacological activities of various potencies have also been found, including, amongst others, inhibition of lipid-peroxidation, mutagenicity of carcinogens and tumor promotion, host-mediated antitumor effects specific to particular tannin structures, antiviral activity and potentiation of antibacterial activity.

Keywords: Hydrolyzable tannins; Polyphenols; Classification of hydrolyzable tannins; Hydrolyzable tannin oligomers; Oxidized polyphenols; Plant evolution; Inhibition of peroxidation, Radical scavenger; Antimutagenicity; Anti-tumor promotion; Host-mediated antitumor activity; Antiviral activity

Abbreviations: ACTH, adrenocorticotropic hormone; ADP, adenine 5′-diphosphate; AIBN, 2,2′-azobisisobutyronitrile; B[a]p diol epoxide, ±7β 8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene; DHHDP, dehydrohexahydroxydiphenoyl; DMBA, 7,12-dimethylbenz[a]anthracene; DMPO, 5,5-dimethyl-1-pyrrolidone-N-oxide; DPPH, 1,1-diphenyl-2-picrylhydrazyl; EVB-EA, Epstein-Barr virus early antigen; ECG, (−)-epicatechin gallate; EGCG, (−)-epigallocatechin gallate; ENNG, *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine; ESR, electron spin resonance; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HHDP, hexahydroxydiphenoyl; 5-HETE, 5-hydroxy-6,8,11,14-eicosatetraenoic acid; 5-HPETE, 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid; MM2, mouse mammary cancer 2; MNNG, *N*-methyl-*N*′-nitroso[4,3-b]indole; NADPH, nicotinamide adenine dinucleotide phosphate; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; *N*-OH-Trp-P-2, 3-hydroxyamino-1-methyl-5H-pyrido[4,3-b]indole; RA, relative astringency; RAG, astringency relative to that of geraniin; RMB, relative affinity to methylene blue; RMBG, affinity to methylene blue relative to that of geraniin; TNF-α, tumor necrosis factor-α; TPA, 12-*O*- tetradecanoylphorbol 13-acetate; XOD, xanthine oxidase.

☆ The Tannin Conference Award Address at the 4th Tannin Conference, of the Fall Meeting of the American Chemical Society, Philadelphia, PA, USA, 22–26 August 2004.

[1] Present address: Kitakata 3-4-25, Okayama 700-0803 Japan.
* Tel./fax: +81 86 223 2502.
E-mail address: okudatakjp@ybb.ne.jp.

0031-9422/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2005.04.023

Contents

1. Introduction

Many tannin-rich medicinal and food plants have been appreciated for their beneficial effects without being troubled by any obvious toxicity (Okuda et al., 1992a). Research on the tannins in traditional medicinal plants, presented here, started (Okuda et al., 1975, 1991, 1992a,b, 1995, 1999a; Yoshida et al., 2000) when the chemical, biological and pharmacological properties of tannins in most medicinal plants were not yet subjected to modern analyses.

2. Dehydroellagitannins and their oxidized congeners in *Geranium thunbergii*

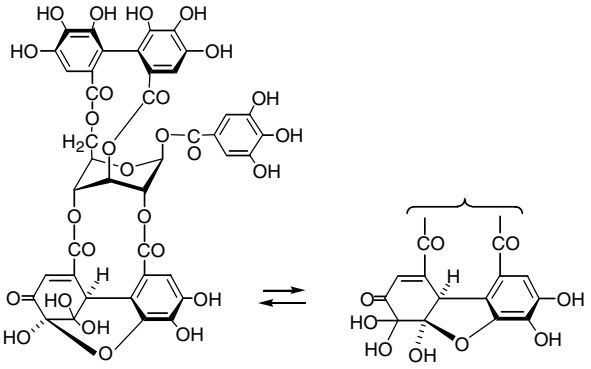
A crystalline tannin named geraniin (**1**), the main component accounting for over 10% of the dry leaf

weight of *Geranium thunbergii* (Okuda et al., 1980a), was isolated from this popular Japanese medicinal plant. The plant is an official medicine in the Japanese Pharmacopoeia (Okuda, 1999c) and is used for the treatment of diarrhea and for controlling intestinal function. This finding was followed by isolation of many other tannins from various medicinal plants.

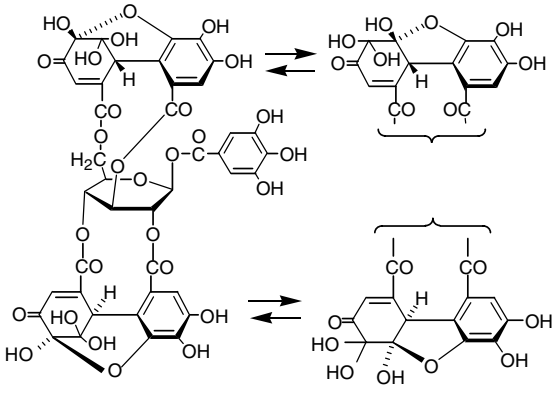
2.1. Geraniin (*1*), a crystalline tannin with low astringency

Geraniin (**1**) surprisingly showed almost no astringency on the human tongue, while its potency in binding with protein and basic substances, as expressed by the RA and RMB values, was comparable with that of tannic acid (Okuda et al., 1985), a gallotannin mixture from Chinese gall (Haslam, 1989). This property of geraniin (**1**) showed that the binding potency of a tannin is not always accompanied by a recognizable astringent taste (Okuda et al., 1977a, 1978), and that the desirability of *G. thunbergii* is partially attributable to this mild property of geraniin (**1**).

The chemical structure of geraniin (**1**) was first determined by chemical and spectroscopic methods (Okuda et al., 1977b, 1980b, 1982a,c,d, 1989), together with subsequent X-ray crystallographic analysis which revealed that seven moles of water were hydrogen-bonded (Luger et al., 1998). Geraniin (**1**) is also found in most *Geranium* species, as well as in many species of the Euphorbiaceae, and *Erythroxylum coca* (Okuda et al., 1980a) (Fig. 1).



Geraniin (**1**)



Dehydrogeraniin (**2**)

Fig. 1. Geraniin (**1**) and Dehydrogeraniin (**2**).

2.2. Structural complexity of dehydroellagitannins in solution

The spectroscopic (Okuda and Yoshida, 1980) and chromatographic (Hatano et al., 1988a) complexities caused by the presence of the dehydrohexahydroxydiphenoyl (DHHDP) group in geraniin (**1**), affording the two tautomers, are further multiplied in the molecules of some minor components in the same plant, namely dehydrogeraniin (**2**) and furosinin (**3**). Dehydrogeraniin (**2**) forms a mixture of four tautomers by equilibration of its two DHHDP groups, and furosinin (**3**) is equilibrated among eight tautomers due to anomerization (Okuda et al., 1982b) (Fig. 2).

A highly water soluble condensate of geraniin (**1**) with ascorbic acid was isolated from the mother liquor after removal of the other tannins by extraction with organic solvents. This condensate, ascorgeraniin (elaeocarpusin) (**4**), was readily synthesized from a mixture of geraniin (**1**) and ascorbic acid in a weakly acidic aqueous solution at room temperature, demonstrating the likely way of its in vivo formation (Okuda et al., 1986a,b). The high water-solubility of (**4**) may also imply that the often-occurring solubilization in plant cells and extracts of tannins which are insoluble when isolated in pure form, may be at least partially attributable to their condensation or adduct formation with some co-existing substances.

3. Oxidative transformations of polyphenol groups in tannins and their classification based on the degree of oxidation

Monomeric hydrolyzable tannins can be classified according to the degree of oxidation as follows.

3.1. Ellagitannins, dehydroellagitannins and their oxidized congeners

Geraniinic acids B (**5**) and C (**6**), in which the DHHDP group present in geraniin (**1**) has been further oxidized, were also isolated from *G. thunbergii* as minor components (Ito et al., 1999a). Some examples of hydrolyzable tannins having a hexahydroxydiphenoyl (HHDP) group, a DHHDP group, their enantiomers, and their oxidized congeners, isolated from various medicinal plants are as follows: mallotusinic acid (**7**) accompanied by geraniin (**1**) from *Mallotus japonicus* leaf, a folk medicine for gastric ulcer, whose bark extract

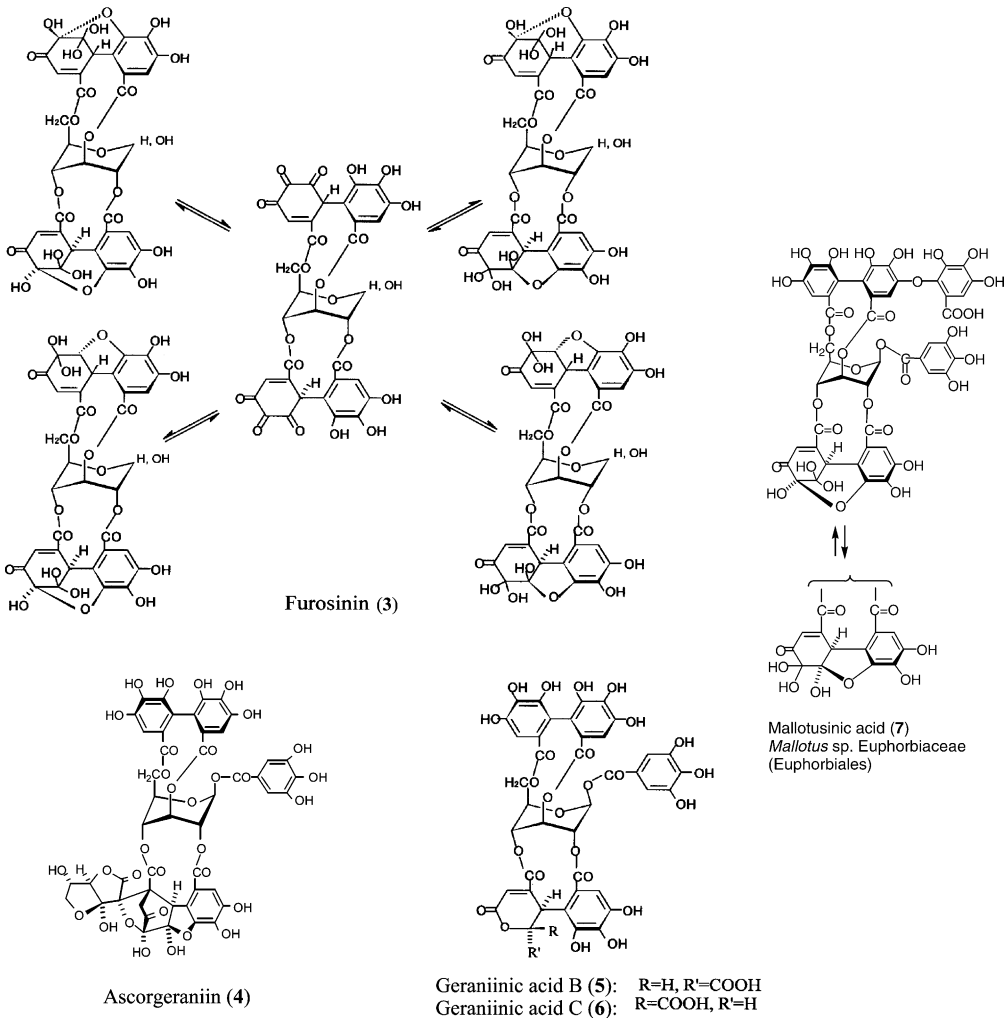


Fig. 2. Furosinin (**3**), Ascorgeraniin (**4**), Geraniinic acids B (**5**) and C (**6**), and Mallotusinic acid (**7**).

is a clinically used medicine in Japan (Okuda et al., 1980b; Okuda and Seno, 1981), as well as being produced by some species in the Euphorbiaceae (Okuda et al., 1980a); granatin B from the fruit peel of *Punica granatum*, which is used for sore throat and diarrhea in East Asia (Okuda et al., 1980c); and isoterchebin having an enantiomeric DHHDP group, which together with several oligomers (shown later) from the fruit of *Cornus officinalis*, is a tonic used in traditional Chinese medical prescriptions (Okuda et al., 1981a). Terchebin, isoterchebin, chebulinic acid and chebulagic acid (**8**) having a DHHDP group or its oxidized congener (named chebuloyl) from myrobalans (*Terminalia chebula*), frequently used in Ayurveda medicine in India and Southeast Asia, and for leather tanning, were structurally characterized, including their absolute configurations (Okuda et al., 1980c; Yoshida et al., 1980, 1982a) and have resulted in revision of postulated structures (Schmidt, 1956; Haslam and Uddin, 1967). Phyllanthusiins A (**9**), B (**10**) and C (**11**), and repandusinic acid (**12**) in *Phyllanthus flexuosus* have several varieties of oxidized congeners of the DHHDP group in each molecule (Yoshida et al., 1992a) (Fig. 4).

These polyphenolic functionalities, found in various tannins (Okuda et al., 1995) were classified into types I–IV (Fig. 3) according to their oxidation level, and into types I+ to IV+ considering additional structural transformations as exemplified by **14**–**18** in Figs. 5 and 6 (Okuda et al., 2000).

3.2. Complex tannins and other C-glycosidic tannins

Complex tannins in which an ellagitannin and a flavan-3-ol are bound by a *C*-glycosidic linkage belong to type II+ tannins. Examples include camelliatannins A (**19**), B, C and E from *Camellia japonica* leaf (Hatano et al., 1991a, 1995) and malabathrins A, E and F from *Melastoma malabathricum* (Yoshida et al., 1992b). A complex tannin, which is a gallate of a regular glucoside of a flavan-3-ol having a phloroglucinol residue, was isolated from *Glochidion rubrum* (Chen et al., 1995). The complex tannins, guavins A, C and D, were accompanied

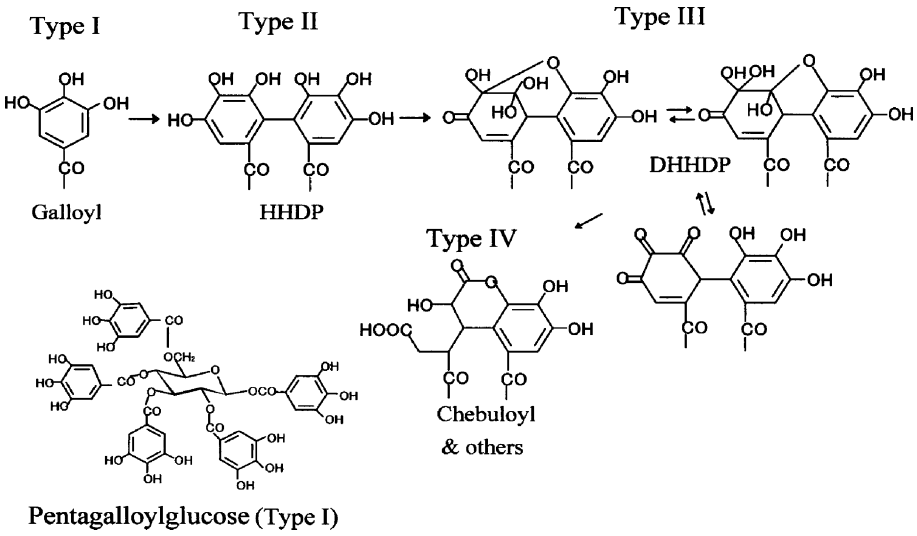


Fig. 3. Types I–IV polyphenolic functionalities and a type I tannin.

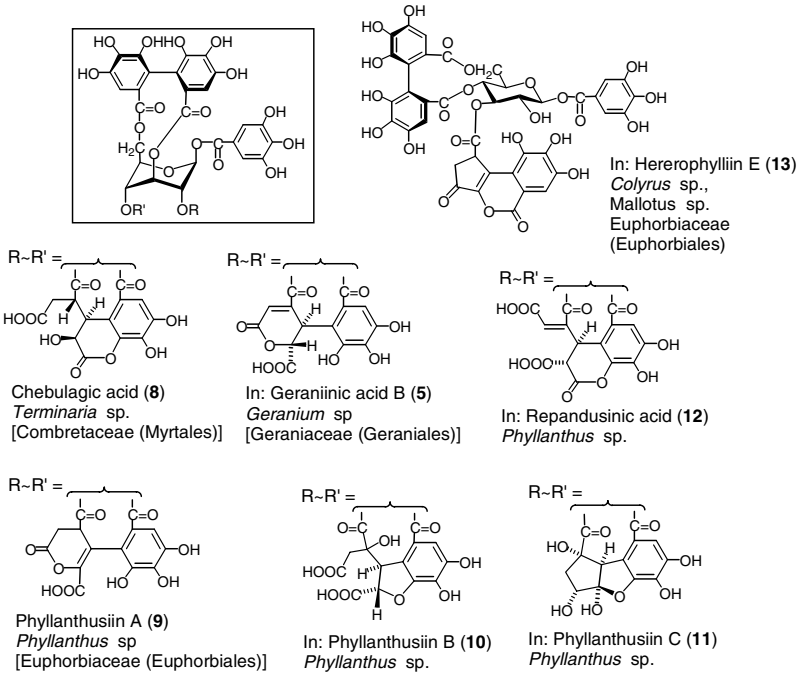


Fig. 4. Examples of type IV polyphenolic functionalities and tannins.

in *Psidium guajava* (Okuda et al., 1987a) by guavin B, a dihydroxybenzophenone glucosidic ellagitannin (Okuda et al., 1984c) (see Figs. 6 and 7).

The *C*-glycosidic tannin structures lacking a flavan-3-ol unit, found earlier in castalagin and vescalagin and analogs isolated from the wood of *Castanea* and *Quercus* species (Mayer, 1971), were later reported in a variety of structures such as casuarinin (**15**), stachyurin (**16**) and casuariin (**20**) from species in the Casuarinaceae, Stachyuraceae, Myrtaceae, Betulaceae, Fagaceae, Hamamelidaceae, Lythraceae, Punicaceae, Melastomataceae, Rosaceae, Elaeagnaceae, Theaceae, Juglandaceae (Okuda et al., 1981b, 1982f,g, 1993a), and others.

4. Oligomeric hydrolyzable tannins

The first hydrolyzable tannin oligomer identified was agrimoniin (**21**), a dimer having α-glucosidic linkages in the monomer units and was isolated from *Agrimonia pilosa*, a plant used for treating diarrhea and hemorrhageing (Okuda et al., 1982e, 1984b). The presence of the oligomeric structures was previously indicated by a color reaction (Bate-Smith, 1972). The oligomers have been found to be widely distributed in medicinal plants. They posses a variety of structures, examples being gemins A, B and C (dimers) from *Geum japonicum*, an anti-inflammatory agent and a diuretic (Yoshida et al., 1982b,d,

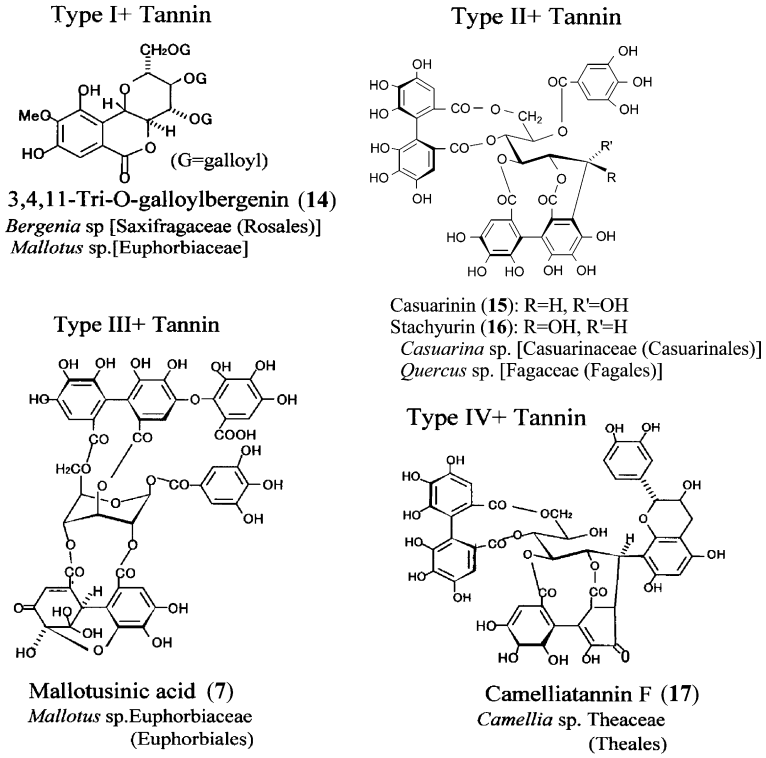


Fig. 5. Examples of types I+–IV+ tannins.

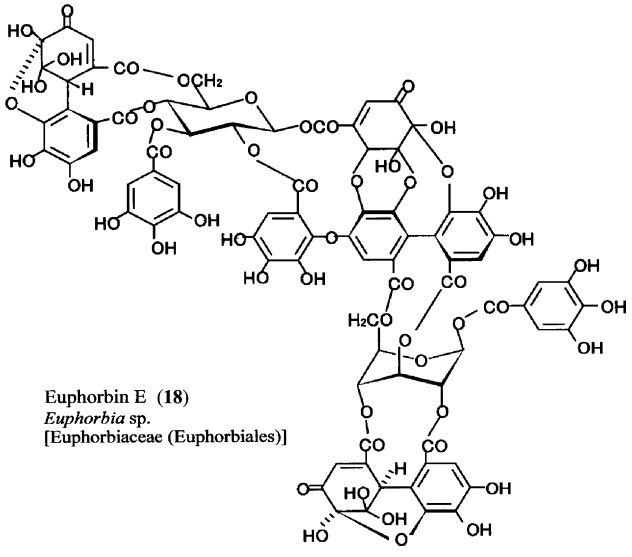


Fig. 6. An example of type III+ tannin [Euphorbin E (**18**)].

1985a), rugosins D, E and F (dimers) from *Rosa rugosa*, an antidiarrheic medicinal plant (Hatano et al., 1990c), cornusiins A (dimer), C (trimer), D, E (dimers) and F (trimer) from *Cornus officinalis* (Okuda et al., 1984d; Hatano et al., 1989a,b, 1990e), and malabatrins B, C and D from *Melastoma malabathricum* (Yoshida et al., 1992c).

Several tetramers, e.g., trapanin B (**22**) from *Trapa japonica*, a tonic (Hatano et al., 1990a), nobotanin K from melastomataceous plants (Yoshida et al., 1989c), and hirtellin Q_1 (along with a trimer, hirtellin T_1 and a dimer, hirtellin G) from *Reaumuria hirtella* (Ahmed et al., 1994b), as well as a pentamer from *Monochaetum multiflorum* (Jose et al., 2001) were also identified.

A variety of dimers possessing a dehydroellagitannin functionality, e.g., euphorbins A and B (condensate of geraniin and an oligogalloylglucose), euphorbin E (**18**) from *Euphorbia hirta* (Yoshida et al., 1988, 1990c), and euphorbin F, comprising geraniin and tellimagrandin II (1,2,3-tri-*O*-galloyl-4,6-*O*-HHDP-glucose), from *Euphorbia tirucalli* (Yoshida et al., 1991b), were also isolated.

The macrocyclic oligomers, i.e. oenotheins A (**23**) (trimer) and B (**24**) (dimer) from *Oenothera erythrosepara*, a medicinal plant of native Americans (Yoshida et al., 1991a; Hatano et al., 1990d), and woodfordins A, B, C (dimers) (Yoshida et al., 1989a, 1990a) and D (trimer) (Yoshida et al., 1991a) from *Woodfordia fruticosa*, an Indonesian medicinal plant, exhibited notable host-mediated antitumor activity. Their activity may partially be due to restriction of the molecular conformation by macro-ring formation. Camelliin B from several species of theaceous plants (Yoshida et al., 1990b), and tamarixinin B from *Tamarix pakistanca* (Yoshida et al., 1993) are also macrocyclic dimers. A macrocyclic dimer having a DHHDP group was isolated from *Eugenia uniflora* (Lee et al., 1997) and the macrocyclic trimer, hirtellin T_2, from *Reaumuria hirtella* and *Tamarix pakistanica* (Ahmed et al., 1994a).

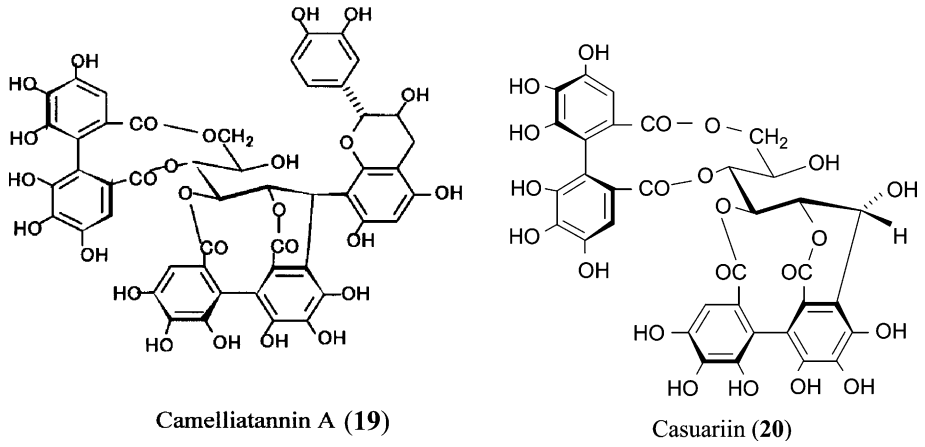


Fig. 7. Camelliatannin A (**19**) and Casuariin (**20**).

These tannins may be classified into types II+ (agrimoniin, etc.) or III+ (euphorbins A, etc.) (see Fig. 8).

5. Classification of hydrolyzable tannin oligomers based on the linking unit

Hydrolyzable tannin oligomers can also be classified by the linking unit between two monomers. The linking units composed of two galloyl groups are classified into *p*-GOG, *m*-GOG and several types of GOGOG units, etc. by the location of the hydroxyl group participating in the ether linkage (Okuda et al., 1993a). The *m*- and *p*-DOG units comprise an HHDP and a galloyl group, and the HHDP group provides the ether oxygen from its *m*- and *p*-hydroxyl functions (Fig. 9). Trapanin B (**22**) is a tetramer in which the monomeric units are linked via three *m*-DOG functionalities (Hatano et al., 1990a).

The $D(OG)_2$ unit possesses an additional galloyl group on the HHDP moiety of the DOG unit, as exemplified by oenothein A and woodfordin D from *Woodfordia fruticosa* (Yoshida et al., 1991a).

In the GOD units, the galloyl group provides the ether oxygen.

6. Hydrolyzable tannins as chemotaxonomic markers, and the correlation of their oxidation stage with plant evolution

Because of the specificity of hydrolyzable tannin structure and the producing plant species, the tannins can be used as chemotaxonomic markers as found in the Rosaceae (Okuda et al., 1992c). The oxidation levels of the polyphenolic moieties in hydrolyzable tannin molecules can also be correlated with the plant evolution system of the Dicotyledoneae (Okuda et al., 2000). This correlation with Cronquist's evolution system shows that only types I, II and II+ tannins are produced in the Magnolidae and Caryophillidae as well as lower subclasses in the Dicotyledoneae, whereas type III, III+ and IV tannins are additionally found in the Rosidae, a highly developed subclass in the Dicotyledoneae (Fig. 10). This kind of correlation is also found in each subclass (Okuda et al., 2000).

7. Seasonal transformation of tannin structures in *Liquidambar formosana* leaves, and hydrolyzable tannin production in callus cultures

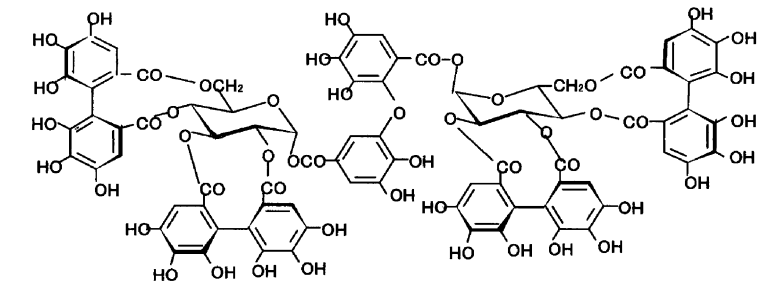
The hydrolyzable tannin profile in a plant species is generally unchanged throughout the year. However, marked seasonal transformations were found in the leaves of *Liquidambar formosana*. Tellimagrandin II (**25**), casuarictin (**26**) and pedunculagin (**27**) (Okuda et al., 1983a) are the main components in Spring leaves, while casuarinin, accompanied by several analogs, were most abundant in Summer and Autumn leaves (Hatano et al., 1986a). Aldehydic liquidambin (**28**) (5-*O*-galloyl-2,3;4,6-di-*O*-(*S*)-hexahydroxydiphenoyl-D-glucose), the most plausible intermediate between pedunculagin and casuarinin was isolated from leaves in May, thus supporting the presumed biotransformation as shown in Fig. 11 (Okuda et al., 1987b).

Gallotannins and ellagitannins are produced in the callus and cell suspension cultures (Yazaki and Okuda, 1989, 1990), but a cell suspension culture of *Geranium thunbergii* produced phyllanthusiin D, which is not found in the intact plant (Yazaki et al., 1991).

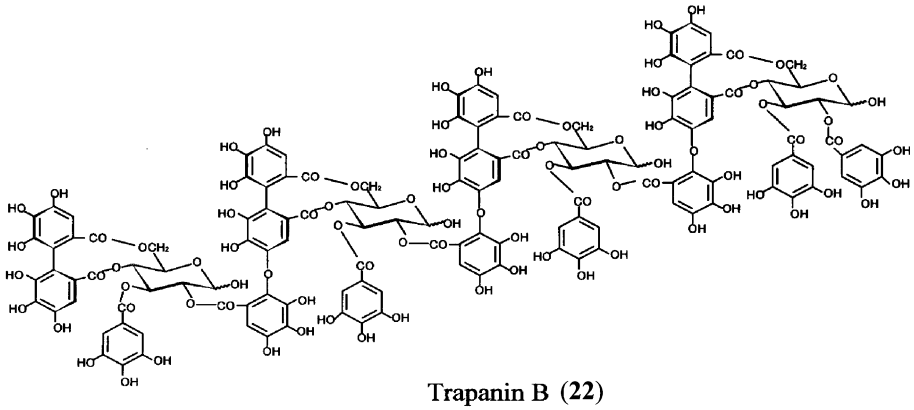
8. Caffeic acid esters with tannin-like activities

8.1. Labiataetannins

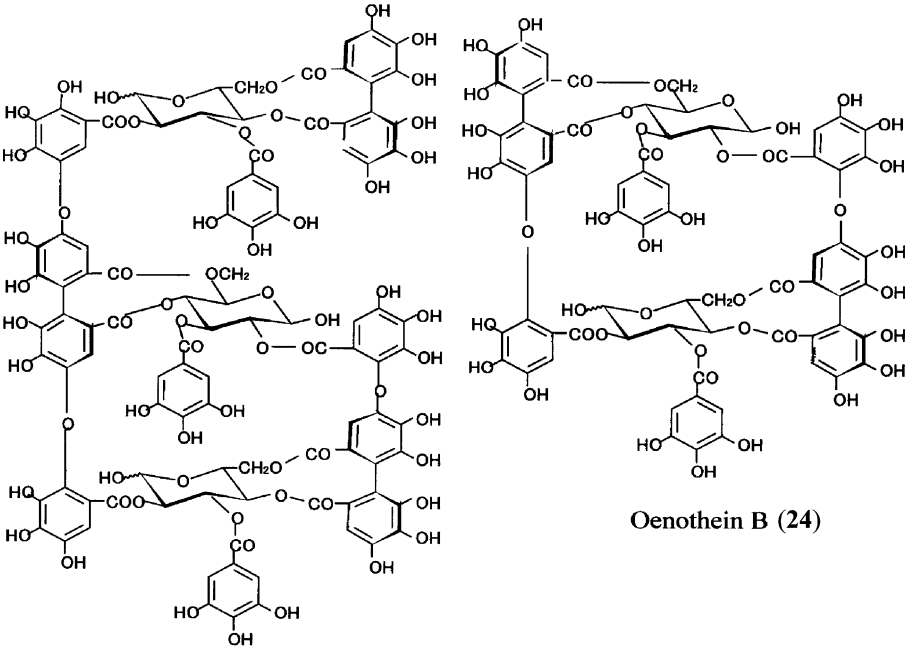
The polyphenols in members of the Labiatae and related families are called labiataetannins. They are the "oligomers" formed by esterification of caffeic acid



Agrimoniin (21)



Trapanin B (22)



Oenothein B (24)

Oenothein A (23)

Fig. 8. Agrimoniin (**21**), Trapanin B (**22**) and Oenotheins A (**23**), B (**24**).

and its hydrated derivative, 3,4-dihydroxyphenyllactic acid. Rosmarinic acid is the main polyphenol in some labiate medicinal herbs in the western world, such as *Rosmarinus officinalis* and *Salvia officinalis*, in some East-Asian labiate medicinal plants, exemplified by *Perilla fructescens* var. *acuta*, a popular spicy vegetable in Japan, and a constituent in traditional Chinese medical prescriptions (Okuda et al., 1986c). Among the trimers are lithospermic acids A and B, while meritiric acids A and B were obtained from *Melissa officinalis* (Agata et al., 1993a) and other labiate medicinal plants. Rabdosiin is a tetramer, found in *Rabdosia japonica*, a traditional stomachic in Japan (Agata et al., 1988, 1989).

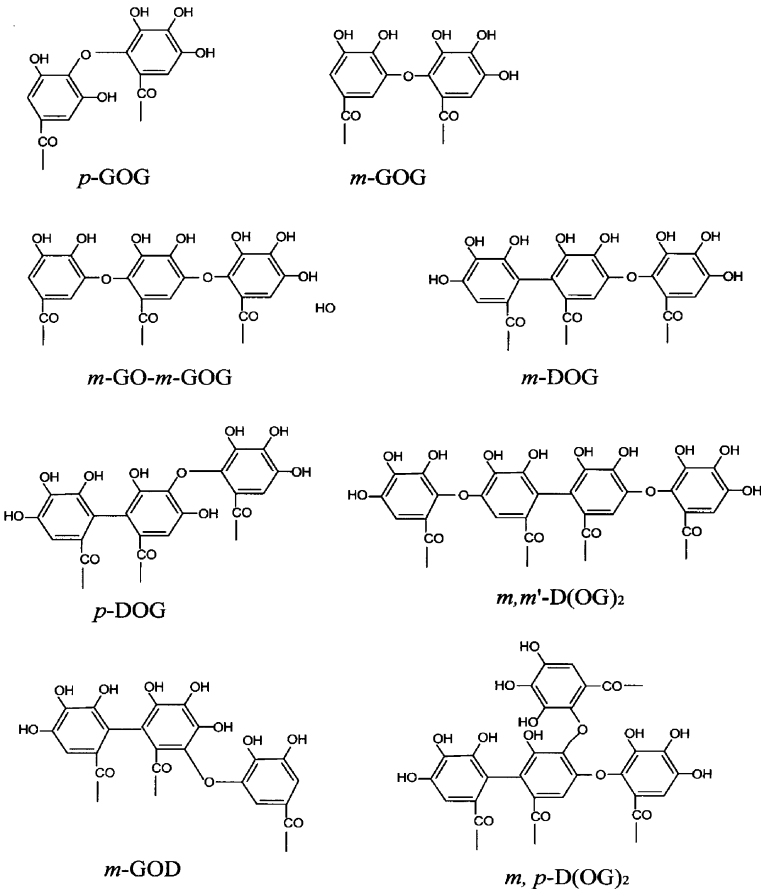


Fig. 9. GOG, DOG, GOD linking units and their derivatives.

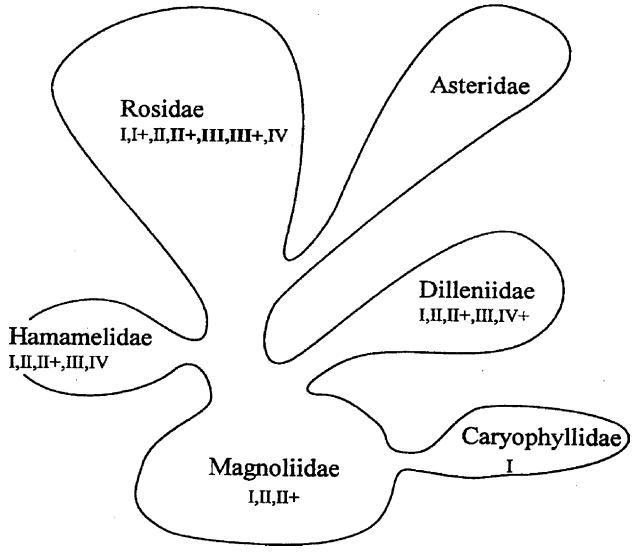


Fig. 10. Correlation of oxidative transformation of tannins with subclasses in Cronquist's system of plant evolution.

8.2. Caffetannins

Chlorogenic acid, 3-caffeoylquinic acid, is the main component of caffetannins in coffee, but 3,5-dicaffeoylquinic acid, accompanied by its 3,4- and 4,5-isomers, is the main component in *Artemisia princeps* and *A. montana*, popular folk medicines and vegetables in Japan (Okuda et al., 1986d). It is notable that dicaffeoylquinic acids, which exhibit markedly higher lipid-peroxidation inhibitory activities than chlorogenic- and caffeic acids, and α-tocopherol (Okuda et al., 1983b; Kimura et al., 1984b; Fujita et al., 1988c) are the main components in these Artemisia species. 1,3,5-Tricaffeoylquinic acid was isolated from *Xanthium strumarium*, which is also a composite medicinal plant used for the treatment of skin diseases (Agata et al., 1993b).

The binding activities of the labiatae- and caffetannins, expressed by their RA and RMB values, are between 1/4 and 1/5 of that of geraniin (**1**) (Okuda et al., 1985), but the inhibitory effect of 3,5-dicaffeoylquinic acid on lipid peroxidation was comparable to those of typical hydrolyzable tannin monomers (Hatano et al., 1984a,b, 1985, 1987; Fujita et al., 1988b).

9. Gallates of flavan-3-ols, their oligomers, other flavonoids, hydroxyquinones and bergenin

Some galloylated flavans and their oligomers in the dicotyledons exhibit biological activities comparable to

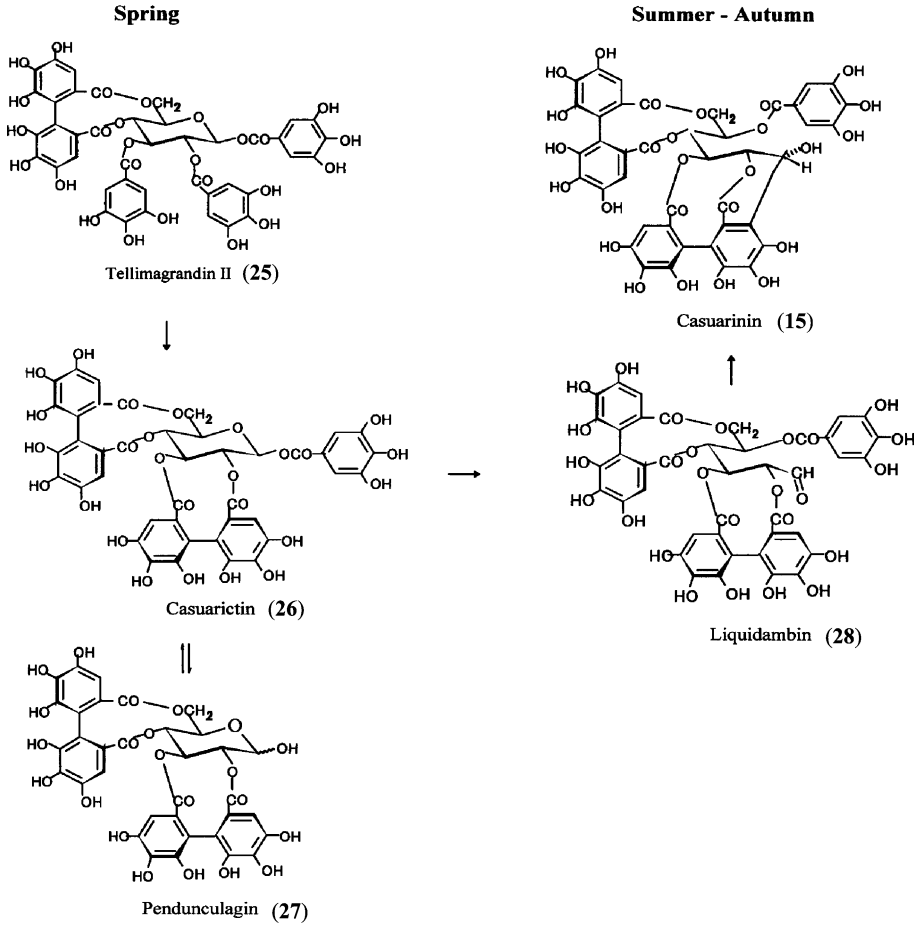


Fig. 11. Seasonal transformation of tannin structures in *Liquidambar formosana* leaf.

those of hydrolyzable tannins. (−)-Epigallocatechin gallate (EGCG), the main polyphenol in green tea, accompanied by (−)-epicatechin gallate (ECG) and other flavan-3-ol analogs, exhibits a binding capacity comparable to those of many hydrolyzable tannins in spite of their small molecular size (Okuda et al., 1985). The inhibitory effects of galloylated flavonoids such as hyperin-2″-*O*-gallate from *Pyrola incarnata* and astragallin-2″-*O*-gallate from *Euphorbia maculata*, a medicinal plant used by native Americans, on xanthine oxidase, were markedly stronger than those of the corresponding flavonoid glucosides (Hatano et al., 1991b). Astragalin-2″,6″-di-*O*-gallate was isolated from *Loropetalum chinense*, an antitussive, hemostat and antidiarrhoeal medicinal plant (Liu et al., 1997).

The proanthocyanidin oligomers isolated from *Saxifraga stolonifera*, an edible medicinal plant in Japan, were galloylated (96%) at *O*-3 of the epicatechin unit (Hatano et al., 1986b). The activities of EGCG and ECG in suppressing superoxide anion radical ranked amongst the highest of the screened polyphenols, and the activities of trimeric and tetrameric (−)-epicatechin gallate derived procyanidins from *Saxifraga stolonifera* were as potent as those of the hydrolyzable tannins (Hatano et al., 1989c). The scavenging activities of these tri- and tetramers on the DPPH radical were also comparable to those of typical hydrolyzable tannins (Hatano et al., 1989c).

The fruits of *Diospyros kaki* (akin to persimmon) also contain proanthocyanidin oligomers based on catechin, gallocatechin, catechin-3-*O*-gallate, gallocatechin-3-*O*-gallate and unknown terminal residues (Matsuo and Itoo, 1978). Sweet fruits of several cultivated forms in which tannins are rendered insoluble are popular autumn fruits in Japan and are considered to reduce alcoholic intoxication. Fermented fruit juice from the wild Diospyros species is used as a dye, an antiseptic, a waterproofing agent, and a folk medicine against hypertension. Rhubarbs, rhizomes of several Rheum species, are purgatives, and also ingredients in traditional Chinese medical prescriptions. They contain procyanidins that are galloylated to various extents (Okuda et al., 1981c; Kashiwada et al., 1986), and are regarded as participants in controlling digestive

organs. The purgative components of rhubarbs are sennosides A and B.

Gallates of various flavonoids and related phenolics showing appreciable biological activities have been isolated from medicinal plants. Examples are bergenin gallates and demethylbergenin gallate from the bark of *Mallotus japonicus* (Yoshida et al., 1982c). This species is used clinically against gastric ulcers in Japan. In addition, galloylarbutin was obtained from *Bergenia purpurascens*, a haemostatic and tonic (Chen et al., 1987), and galloylhomoarbutin from *Pyrolla incarnata* (Yazaki et al., 1989). The RMBG [RMB value relative to that of geraniin (**1**)] value (1.30) of galloylhomoarbutin was comparable to those of several hydrolyzable tannin monomers and oligomers, and higher than that of tannic acid from Chinese gall.

10. Fundamental activities of tannins – binding, reducing and antioxidant activities

The colorimetry of chemically characterized tannins of various structures was developed using hemoglobin as the substrate (Okuda et al., 1977a), a procedure which was previously suggested by Bate-Smith (1973). The utility of this assay was enhanced by the use of methylene blue which significantly reduced the amount of tannin sample required for the assay (Okuda et al., 1985). The relative astringency (RA) and relative affinity to methylene blue (RMB) values establish the binding potency of each tannin, and are also useful for quantification of tannin content. Comparisons of each biological and pharmacological activity with these binding activities were useful in the studies of the mechanism of the various activities of tannins (Okuda et al., 1983b; Hatano et al., 1989c).

Tannins were found to reduce co-existing substances under mild conditions. Metallic ions, such as Cr^{6+}, Fe^{3+} and Cu^{2+}, were reduced to Cr^{3+}, Fe^{2+} and Cu^{+}, respectively, by mixing with tannin solutions at room temperature (Okuda et al., 1982h).

Inhibition of peroxidation is one of the most important activities underlying the health effects of tannins (Okuda, 1997, 1998, 1999b).

11. Inhibition of lipid peroxidation in animals and the effects on arachidonate metabolism, the activities underlying the health effects of tannins

The discovery of the inhibitory effects of tannins on lipid peroxidation in rat liver mitochondria and microsomes was followed by the uncovering of several effects related to improving the symptoms caused by feeding peroxidized oil, and to inhibiting lipoxigenase products in arachidonate metabolism.

11.1. Inhibition of lipid peroxidation in rat liver mitochondria and microsomes, in intact eye lens, and of liver damage by tannins

Lipid peroxidation in rat liver mitochondria stimulated by adenine 5′-diphosphate (ADP) and ascorbic acid, and that in rat liver microsomes stimulated by ADP and nicotinamide adenine dinucleotide phosphate (NADPH), was inhibited by 27 tannins and related polyphenols to various extents (Okuda et al., 1983b). The inhibition by pedunculagin, a molecule possessing two HHDP groups, was the most potent in the former system, and the second most potent in the latter system. EGCG also displayed potent activity.

Lipid peroxidation caused by the xanthin–xanthine oxidase system in the cell membranes of mouse eye lens, a process that induces cataract formation, was potently inhibited by several tannins among which were pentagalloylglucose, geraniin (**1**) and ellagic acid (Iwata et al., 1987). CCl_4-, D-galactosamine- and thioacetamide-induced hepatic injury, and aminonucleoside nephrosis in rats, were also significantly improved by geraniin (**1**) (Nakanishi et al., 1998a,b, 1999a,b).

11.2. Effects on arachidonate metabolism

Inhibition of 5-lipoxygenase in the arachidonate metabolism in leukocytes, evaluated by the level of 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) produced from 5-hydroperoxyeicosatetraenoic acid (5-HPETE), may relieve asthma, inflammation and various allergic conditions caused by leucotrienes derived from 5-HPETE. The inhibition of 5-HETE production shown by geraniin (**1**) was significant. 5-HETE levels were also lowered by some other polyphenols, such as corilagin, 3,5-dicaffeoylquinic acid and rosmarinic acid (Kimura et al., 1986, 1987).

12. Radical scavenging mechanism in the inhibition of lipid peroxidation

The inhibitory effects of tannins on lipid peroxidation, initially found for that in liver mitochondria and microsomes (Okuda et al., 1983b), are due to the free radical scavenging activities of tannins.

12.1. Inhibition of oxidation of methyl linoleate induced by radical chain reactions

The radical chain peroxidation of methyl linoleate induced by photolysis of 2,2′-azobisisobutyronitrile (AIBN), was studied by kinetic and ESR measurements. Tannins generally exhibited longer-lasting inhibitory effects than vitamins C and E, and the

kinetics obtained were explained reasonably well by a scavenging mechanism for peroxy radicals. The in situ ESR detection of tannin radicals showed the signals of each tannin, documenting the radical scavenging effect by tannins (Fujita et al., 1988a,b). A correlation was observed between the intensities of each tannin's inhibitory effect on the peroxidation of methyl linoleate, and the inhibitory potency by each tannin on ADP plus ascorbic acid-induced lipid peroxidation in mitochondria (Okuda et al., 1983b). Similar trends were also found for inhibition of lipoxygenase dependent lipid peroxidation (Fujita et al., 1988c), and for inhibition of autoxidation of ascorbic acid (Fujita et al., 1987).

12.2. Scavenging effects of tannins on DPPH radical

Potent scavenging effects on 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical were exhibited by pentagalloylglucose, tellimagrandins I and II (**25**), pedunculagin (**27**), isoterchebin, mallotusinic acid (**7**), geraniin (**1**) and chebulinic acid, etc., whereas the effects of low molecular weight polyphenols, except for EGCG and ECG, were low. This is in accord with the trends in the antioxidative effects of tannins again supporting the radical-scavenging mechanism (Yoshida et al., 1989b). The intensity of the DPPH signals in the ESR spectra gradually decreased in a dose-dependent manner with increase in geraniin (**1**) concentration, until they were replaced by the signal of a 5,5-dimethyl-1-pyrrolidone-*N*-oxide (DMPO) adduct of a phenoxy radical assignable to each tannin (Hatano et al., 1989c) (see Fig. 12).

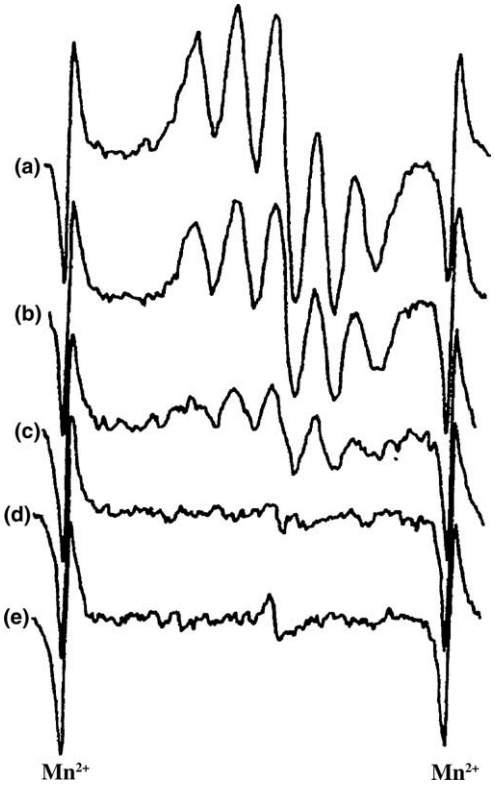


Fig. 12. Scavenging effects of geraniin (**1**) on the ESR spectrum of DPPH. The ESR spectra were recorded in the absence [(a)] and in the presence [(b) 5.0×10^{-7} M, (c) 1.0×10^{-6} M, (d) 2.5×10^{-6} M, (e) 5.0×10^{-6} M] of geraniin (**1**).

12.3. Scavenging effects of tannins on superoxide anion radical generated in the hypoxanthin-xanthin oxidase system

The antioxidative effects of tannins were also determined towards the superoxide anion radical generated in the hypoxanthine-xanthine oxidase (XOD) system. The trend among the tannins inhibiting superoxide anion radical (Hatano et al., 1989c) was entirely different from that inhibiting xanthine oxidase, estimated by uric acid production from hypoxanthine in this system (Hatano et al., 1990b). The former trend, however, was found to be similar to that for the inhibition of

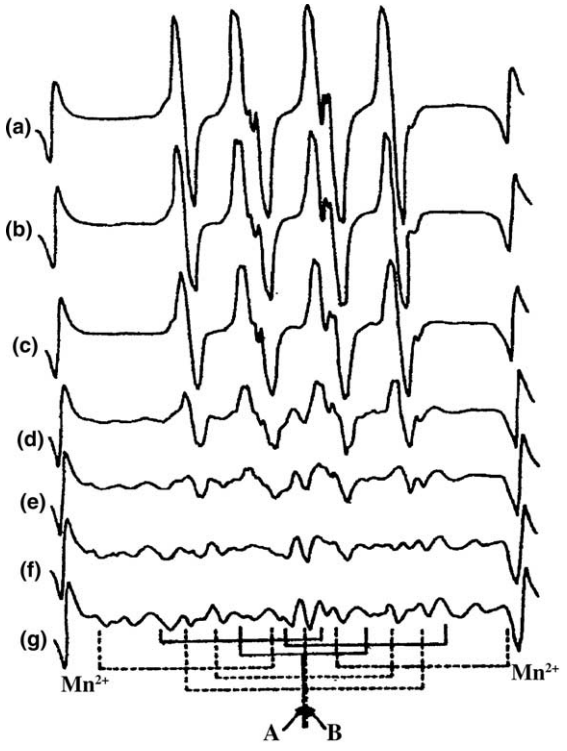


Fig. 13. Scavenging effects of penta-*O*-galloyl-β-D-glucose on the ESR spectrum of the DMPO adduct of superoxide anion radical. The ESR spectra were recorded in the absence [(a)] and in the presence [(b) 1.0×10^{-6} M, (c) 2.5×10^{-6} M, (d) 5.1×10^{-6} M, (e) 1.0×10^{-5} M, (f) 2.5×10^{-5} M, (g) 5.1×10^{-5} M of penta-*O*-galloyl-β-D-glucose. The solid (A) and broken (B) lines below the spectrum (g) indicate the assignments of the hyperfine splitting patterns for the DMPO adduct of a C-centered radical and the hydrogen adduct of DMPO (DMPO-H), respectively.

lipid peroxidation, again supporting the radical scavenging mechanism. The ESR spectra of the DMPO adduct of superoxide anion radical decreased in intensity with increase in tannin concentration, until these signals were replaced by the signal of a DMPO adduct of a phenoxy radical from each tannin, in a way similar to that observed in the scavenging of DPPH radical (Hatano et al., 1989c; Okuda, 1993b) (see Fig. 13).

13. Antimutagenic activity of tannins on carcinogens

Upon examination of mutagenicity of tannins by the Ames' test, all tannins were shown to be not mutagenic. Conversely, they showed antimutagenic activity on Trp-P-1(+S9), Trp-P-2 (+S9) (mutagens in burned meat) and MNNG (*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine), and also against the direct-acting mutagens, 3-hydroxyamino-1-methyl-5H-pyrido[4,3-b]indole (*N*-OH-Trp-P-2, a metabolically activated form of Trp-P-2), and (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo-[*a*]pyrene (B[*a*]P diol epoxide) to various extents (Okuda et al., 1984a). Pentagalloylglucose and geraniin (**1**) were among the most active tannins. EGCG also exhibited potent antimutagenicity. The boiling water extract of *G. thunbergii* showed its highest activity against *N*-OH-Trp-P-2 when the concentration of geraniin (**1**) was highest, and upon prolonged boiling, the activity was lowered by hydrolysis of geraniin (**1**) into corilagin, ellagic acid and other species (Okuda et al., 1979, 1984a). However, the activity of the solution on B[*a*]P diol epoxide increased upon prolonged boiling, most probably due to the specifically potent antimutagenic activity of ellagic acid on this direct mutagen. The genotoxicity of carcinogens was also suppressed by EGCG (Hayatsu et al., 1992).

14. Anti-tumor promotion effects and chemoprevention of cancer

Upon preliminary testing for inihibition of tumor promotion, EGCG was among the most active polyphenols (Yoshizawa et al., 1992). Because of the high frequency and large amount of tea consumed by humans, the inhibitory effect of tea polyphenols on tumor promotion was then investigated extensively (Fujiki and Okuda, 1992a,b, 1997, 2002).

14.1. Inhibition of skin-tumor promotion by EGCG, pentagalloylglucose, ellagic acid and C-glucosidic ellagitannins

In week 25 of a two-stage carcinogenesis experiment in mouse skin, a number of the tumor bearing mice treated with 7,12-dimethylbenzo[a]anthracene (DMBA) (a tumor initiator) plus teleocidin (a tumor promoter) was reduced to less than a quarter in the mice treated with this combination of tumor initiator and promoter plus EGCG. The average number of tumors per mouse in the EGCG-treated mice was also reduced to about 5% (Fujiki et al., 1992b; Yoshizawa et al., 1987). Similar results were obtained by using either okadaic acid (Yoshizawa et al., 1992), or sarcophytols A and B (Fujiki et al., 1990) as the tumor promoters. Inhibition by penta-*O*-galloyl-β-D-glucose in a two-stage skin carcinogenesis assay using DMBA plus teleocidin reduced the percentage of tumor-bearing mice to about 50%, and the average number of tumors per mouse to ca. 33% (Yoshizawa et al., 1992).

Anti-tumor promoting activity in the two-stage skin carcinogenesis assay with DMBA and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was exhibited by stenophyllanin A and alienanin B, a *C*-glucosidic ellagitannin monomer and dimer, respectively, from *Cowania mexicana*, a medicinal plant of native Americans. These tannins exhibited inhibitory effects comparable to, or stronger than, EGCG in a preliminary test with Epstein-Barr virus early antigen (EVB-EA) activation, and also exhibited anti-tumor promoting activity in the two-stage mouse skin carcinogenesis assay with DMBA and TPA (Ito et al., 1999b). These observations suggest that there may be other tannins that have anti-tumor promoting activity.

14.2. Tumor inhibition in the gastrointestinal tract by EGCG, and incorporation of EGCG into cells

Inhibition of tumor promotion in the gastrointestinal tract in a model system of mouse duodenal carcinogenesis with *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine (ENNG), by feeding EGCG, resulted in the reduction of the number of tumor-bearing mice to less than one-third of the control group. The number of tumors-per-mouse was also reduced to about one-third (Fujita et al., 1989).

Incorporation of [^{3}H]EGCG into the cytosol and the nuclei was confirmed by microautoradiography in a study of the inhibition mechanism by flow cytometry (Okabe et al., 1997).

14.3. Inhibition of lung cancer and other tumors by tea polyphenols and ellagic acid

The tea polyphenols inihibited the growth of lung, mammary, and stomach human cancer cell lines (Okabe et al., 1997). Ellagic acid inhibited lung tumorigenesis induced by the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Castonguey et al., 1997).

15. Host-mediated anti-tumor activity – the most structure-specific activity of oligomeric ellagitannins potentiating host-immune defense

Several oligomeric hydrolyzable tannins showed a potent host-mediated anti-tumor effect. Tannins were intraperitoneally (i.p.) injected into mice at 5 or 10 mg/kg 4 days before the i.p. inoculation of Sarcoma-180. More than half of the oligomeric ellagitannins (20 out of 36), and all macrocyclic ellagitannin oligomers showed potent anticancer activity, resulting in a significant increase of 60 day mouse survivors (Miyamoto et al., 1987, 1993a, 1997). The activity of dehydroellagitannins, as either monomers or dimers, was weak. Among the monomers, only tellimagrandin II was active.

Active oligomers were: macrocyclic oligomers such as oenotheins A (**23**) and B (**24**), camelliin B and woodfordins C (Yoshida et al., 1990a,b; Hatano et al., 1990d), D (Yoshida et al., 1991a), E and F (Yoshida et al., 1992d), and also acyclic dimers, such as agrimoniin (**21**), coriariin A and C (from *Coriaria japonica*) (Hatano et al., 1986c), cornusiin A, hirtellins A (Yoshida et al., 1991d) and B (Yoshida et al., 1991c) from *Reaumuria hirtella*, rugosins D and E from *Rosa rugosa* (Hatano et al., 1990c), isorugosin D from *Liquidambar formosana* (Hatano et al., 1988b, 1992) and tamarixinin A from *Tamarix pakistanica* (Yoshida et al., 1991d). Oenothein B (**24**) also inhibited the growth of MM2 ascites tumors and Meth A solid type tumor in mice upon peritoneal administration (Miyamoto et al., 1993c).

This effect, exhibited by injection of tannins either before or after the inoculation of the tumor, is regarded as due to potentiation of the host-immune defense via activation of macrophages (Miyamoto et al., 1993c). This mechanism was supported by their observed interleukin-1β(IL-1β) induction (Miyamoto et al., 1993b).

16. Enhancing and suppressing effects of tannins on enzymes, proteins, peptides and amines

Tannins at low concentration sometimes enhance the activities of enzymes and hormones, although they usually inhibit the activities of enzymes at moderate or high concentrations. The activity of glucosyltransferase from *Streptococcus mutans*, which synthesizes glucan, was enhanced by galloylglucoses at about 10^{-5} M, although this activity was suppressed at a higher concentration of galloylglucose (Kakiuchi et al., 1986).

Adrenocorticotropic hormone (ACTH)-induced lipolysis was enhanced by geraniin (**1**), mallotusinic acid, chebulinic acid and tellimagrandin I at 5–100 μg/ml (Kimura et al., 1983). The production of prostaglandin E_2 from cyclooxygenase in arachidonate metabolism was enhanced by 3,4-di-*O*-caffeoylquinic acid and other caffeates and caffeic acid in a concentration-dependent fashion (Kimura et al., 1987). Histamine release from rat peritoneal mast cells induced by compound 48/80 and also by concanavalin A plus phosphatidylserine was inhibited by the caffetannins from *Artemisia* species (Kimura et al., 1985).

Mouse mammary tumor virus gene expression by poly(ADP-ribose)glycohydrolase, which plays an important role in regulation of gene activation, was profoundly suppressed by tannins among which the tetramer, nobotanin K of molecular weight 3745, isolated from *Heterocentron roseum*, a Mexican melastomataceous plant (Yoshida et al., 1989c), exhibited the highest activity (Tsai et al., 1991, 1992; Aoki et al., 1993). It is noteworthy that the suppressing activity of this tetramer was about 5, 16 and 34 times that of trimers, dimers and monomer, respectively.

Granulocytic cell iodination (incorporation of radioactive iodine into an acid-insoluble fraction) of human peripheral blood polymorphonuclear cells, and also interleukin 1 (IL-1) production, were stimulated by tannins (Sakagami et al., 1990, 1992).

Geraniin (**1**) and corilagin, as well as EGCG, potently inhibited release of tumor necrosis factor-α (TNF-α) (Okabe et al., 2001) in an assay for screening cancer-preventive agents (Fujiki et al., 1998, 2000), again suggesting that tannins of various structures, besides EGCG, could prevent cancer. The inhibition of TNF-α release in macrophages by hydrolyzable tannins and proanthocyanidins, along with their antileishmanial activity, was also reported (Kolodziej et al., 2001a,b).

The inihibition of carbonic anhydrase, which may be applicable to the treatment of glaucoma and diuresis, was exhibited by punicalin, punicalagin, granatin B and gallagyldilactone, isolated from *Punica granatum* (Satomi et al., 1993).

17. Antiviral activities exhibited by hydrolyzable tannins, and induction of DNA fragmentation and apoptosis by gallic acid

Monomeric and dimeric hydrolyzable tannins potently inhibited Herpes simplex virus (Fukuchi et al., 1989). Anti-human immunodeficiency virus (HIV) activity was exhibited (Nakashima et al., 1992; Sakagami et al., 1999) by several hydrolyzable tannins, such as gemin D (monomer) (Yoshida et al., 1985b), nobotanin B (dimer) (Yoshida et al., 1987), camelliin B (dimer) (Yoshida et al., 1990b) and trapanin B (**22**) (tetramer) (Hatano et al., 1990a). In contrast to several biological activities exhibited by the high molecular weight tannins, gallic acid was the most active species in induction of DNA fragmentation and apoptosis, while the activities of the larger tannins were lower (Sakagami et al., 1995, 1997, 1999; Inoue et al., 1994). Gallic acid induced apoptotic cell death in human promyelocytic leukemia

HL-60 cells, whereas high molecular weight tannins were inactive. The possibility that gallic acid may act as a prooxidant in inducing apoptosis was proposed by Sakagami et al. (1997).

18. The effects of orally dosed geraniin (1) on serum lipids, and bioavailability of orally dosed gallates and ellagitannins

The effects on the digestive system underscore some of the most widely utilized applications of tannin-rich medicinal plants. Orally dosed geraniin (**1**) inhibited elevation of serum glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lipid peroxide levels and the atherogenic index in mice in which lipid peroxidation was caused by feeding peroxidized oil (Kimura et al., 1984a). Pretreatment of a gastric ulcer that was induced by HCl-EtOH with geraniin (**1**) significantly reduced the ulcer size (Nakanishi et al., 1991).

Absorption of gallates and ellagitannins from the stomach has been shown by several experiments. ^{3}H-EGCG per os intubation into mice stomachs resulted in detection of radioactivity in the blood 1 h later, and in excreted EGCG 6 h later. The radioactivity was found in the liver, kidney, brain and lung, thus showing incorporation of ^{3}H-EGCG into various organs (Suganuma et al., 1998). Excretion of 3-*O*- and 8-*O*-glucuronides of 3-hydroxy-6-*H*-dibenzo[*b*,*d*]pyran-6-one, and also of 3,8-dihydroxybenzo[*b*,*d*]pyran-6-one were found in the urine and serum of sheep fed with *Terminalia oblongata* leaves (Okuda et al., 1995).

19. Additional effects of tannins

Helicobacter pylori, which is suspected to induce gastric ulcer, was inhibited by several hydrolyzable tannins (Funatogawa et al., 2004). The effectiveness of β-lactams on methicillin-resistant *Staphylococcus aureus* was restored by corilagin, tellimagrandin I and EGCG (Shimizu et al., 2001; Shiota et al., 1999, 2000; Hatano et al., 2003). Superoxide-induced histamine release from rat peritoneal mast cells was inhibited by several hydrolyzable tannins (Kanoh et al., 2000; Yoshida et al., 1999).

20. Conclusions

Tannins of various chemical structures occurring in medicinal and food plants that are utilized world-wide showed several remarkable biological and pharmacological activities that are often very specific to certain tannin structures, and significant for human health. These tannins are thus worthy of further extensive investigations, not only in phytochemistry, but also regarding their health effects.

Acknowledgements

The author wishes to express his sincere thanks for invaluable guidance and collaboration by the following eminent scholars: The late Profs. H. Abe, S. Arichi, S. Iwata, and Drs. and Profs. H. Fujiki, Y. Fujita, H. Hayatsu, S. Kashino, Y. Kimura, R. Koshiura, K. Miyamoto, P. Luger, H. Okuda, H. Sakagami, K. Miyamoto, K.-Y. Yen, L.-L. Yang, and the staff and students at Okayama University.

References

Agata, I., Hatano, T., Nishibe, S., Okuda, T., 1988. Rabdosiin, a new rosmarinic acid dimer with a lignan skeleton, from *Rabdosia japonica*. Chem. Pharm. Bull. 36, 3223–3225.

Agata, I., Hatano, T., Nishibe, S., Okuda, T., 1989. A tetrameric derivative of caffeic acid from *Rabdosia japonica*. Phytochemistry 28, 2447–2450.

Agata, I., Kusakabe, H., Hatano, T., Nishibe, S., Okuda, T., 1993a. Melitric acids A and B, new trimeric caffeic acid derivatives from *Melissa officinalis*. Chem. Pharm. Bull. 41, 1608–1611.

Agata, I., Goto, S., Hatano, T., Nishibe, S., Okuda, T., 1993b. 1,3,5-Tri-*O*-caffeoylquinic acid from *Xanthium strumarium*. Phytochemistry 33, 508–509.

Ahmed, A.F., Memon, M.U., Yoshida, T., Okuda, T., 1994a. Four new trimeric hydrolyzable tannins from *Reaumuria hirtella* and *Tamarix pakistanica*. Chem. Pharm. Bull. 42, 254–264.

Ahmed, A.F., Yoshida, T., Okuda, T., 1994b. New dimeric, trimeric and terameric ellagitannins from *Reaumuria hirtella*. Chem. Pharm. Bull. 42, 246–253.

Aoki, K., Nishimura, K., Abe, H., Maruta, H., Sakagami, H., Hatano, T., Okuda, T., Yoshida, T., Tsai, Y.-J., Uchiumi, F., Tanuma, S., 1993. Novel inhibitor of poly(ADP-ribose)glycohydrolase. Biochim. Biophys. Acta 1158, 251–256.

Bate-Smith, E.C., 1972. Detection and determination of ellagitannins. Phytochemistry 11, 1153–1156.

Bate-Smith, E.C., 1973. Haemanalysis of tannins: The concept of relative astringency. Phytochemistry 12, 907–912.

Castonguey, A., Gali, H.U., Perchellet, E.M., Gao, X.M., Boukharta, M., Jalbert, G., Okuda, T., Yoshida, T., Hatano, T., Perchellet, J.-P., 1997. Antitumorigenic and antipromoting activities of ellagic acid, ellagitannins and oligomeric anthocyanin and procyanidin. Int. J. Oncol. 10, 367–373.

Chen, X.-M., Yoshida, T., Hatano, T., Fukushima, M., Okuda, T., 1987. Galloylarbutin and other polyphenols from *Bergenia purpurascens*. Phytochemistry 26, 515–517.

Chen, L.-G., Yang, L.-L., Yen, K.-Y., Hatano, T., Yoshida, T., Okuda, T., 1995. New hydrolyzable tannins having phloroglucinol residue from *Glochidion rubrum* Blume. Chem. Pharm. Bull. 43, 2088–2090.

Fujiki, H., Suganuma, M., Suguri, H., Takagi, K., Yoshizawa, S., Ootsuka, A., Tanooka, H., Okuda, T., Kobayashi, M., Sugimura, T., 1990. In: Kuroda, Y., Shankel, D.M., Waters, M.D. (Eds.), Antimutagenesis and anticarcinogenesis mechanisms II. Plenum Press, New York, pp. 205–212.

Fujiki, H., Okuda, T., 1992a. (−)-Epigallocatechin gallate. Drugs Future 17, 462–464.

Fujiki, H., Yoshizawa, S., Horiuchi, T., Suganuma, M., Yatsunami, J., Nishiwaki, S., Okabe, S., Nishiwaki-Matsushima, R., Okuda, T., Sugimura, T., 1992b. Anticarcinogenic effects of (−)-epigallocatechin gallate. Preventive Med 21, 503–509.

Fujiki, H., Komori, A., Suganuma, M., 1997. Chemoprevention of cancer. In: Bowden, T., Fischer, S. (Eds.), Comprehensive toxicology. Elsevier, UK, pp. 453–471.

Fujiki, H., Suganuma, M., Okabe, S., Sueoka, N., Komori, A., Sueoka, E., Kozu, T., Tada, Y., Suga, K., Imai, K., Nakachi, K., 1998. Cancer inhibition by green tea. Mutation Res. 402, 307–310.

Fujiki, H., Suganuma, M., Okabe, S., Sueoka, E., Suga, K., Imai, K., Nakachi, K., 2000. A new concept of tumor promotion by tumor necrosis factor-α, and cancer preventive agent (−)-epigallocatechin gallate and green tea. Cancer Detect. Prev. 24, 91–99.

Fujiki, H., Suganuma, M., Imai, K., Nakachi, K., 2002. Green tea: cancer preventive beverage and/or drug. Cancer Lett. 188, 9–13.

Fujita, Yu., Komagoe, K., Sasaki, Y., Uehara, I., Okuda, T., Yoshida, T., 1987. Inhibition mechanism of tannins on Cu(II)-catalyzed oxidation of ascorbic acid. Yakugaku Zasshi 107, 17–22.

Fujita, Yu., Komagoe, K., Niwa, Y., Uehara, I., Hara, R., Mori, H., Okuda, T., Yoshida, T., 1988a. Inhibition mechanism of tannins isolated from medicinal plants and related compounds on autoxidation of methyl linoleate. Yakugaku Zasshi 108, 528–537.

Fujita, Yu., Komagoe, K., Mori, H., Niwa, Y., Okuda, T., 1988b. In situ ESR detection of tannin radicals in tannin-inhibited lipid peroxidation. In: Hayaishi, O., Niki, E., Kondo, M., Yoshikawa, T. (Eds.), Medical, biochemical and chemical aspects of free radicals. Elsevier, Amsterdam, pp. 853–856.

Fujita, Yu., Uehara, I., Morimoto, Y., Nakajima, M., Hatano, T., Okuda, T., 1988c. Inhibition mechanism of caffetannins isolated from leaves of Artemisia species on lipoxygenase dependent lipid peroxidation. Yakugaku Zasshi 108, 129–135.

Fujita, Yo., Yamane, T., Tanaka, M., Kuwata, K., Okuzumi, J., Takahashi, T., Fujiki, H., Okuda, T., 1989. Inhibitory effect of (−)-epigallocatechin gallate on carcinogenesis with *N*-ethyl-*N*-nitro-*N*-nitrosoguanidine in mouse duodenum. Jpn. J. Cancer Res. 80, 503–505.

Fukuchi, K., Sakagami, H., Okuda, T., Hatano, T., Tanuma, S., Kitajima, K., Inoue, Y., Inoue, S., Ichikawa, S., Nonomiya, M., Konno, K., 1989. Inhibition of Herpes simplex virus infection by tannins and related compounds. Antiviral Res. 11, 285–298.

Funatogawa, K., Hayashi, S., Shimomura, H., Yoshida, T., Hatano, T., Ito, H., Hirai, Y., 2004. Antibacterial activity of hydrolysable tannins derived from medicinal plants against *Helicobacter pylori*. Microbiol. Immunol. 48, 251–261.

Haslam, E., 1989. Plant polyphenol. Vegetable tannins revisited. Cambridge University Press, Cambridge.

Haslam, E., Uddin, M., 1967. Some observations on the structure of chebulinic acid and its derivatives. J. Chem. Soc. (C), 2381–2384.

Hatano, T., Yoshida, T., Fujita, Y., Okuda, T., Kimura, Y., Okuda, H., Arichi, S., 1984a. Active tannins in Artemisia species, and their active principles inhibiting lipid peroxidation. J. Med. Pharm. Soc. WAKAN-YAKU 2, 124–125.

Hatano, T., Yoshida, T., Fujita, Y., Okuda, T., Kimura, T., Okuda, H., Arichi, S., 1984b. Effects of tannins from oriental medicinal plants on lipid peroxidation and fat cells. J. Med. Pharm. Soc. WAKAN-YAKU 1, 40–41.

Hatano, T., Okuda, T., Togawa, K., Fujita, Y., Agata, I., Nishibe, S., Kimura, Y., Okuda, H., Arichi, S., 1985. Active tannins in Artemisia species, and their active principles inhibiting lipid peroxidation. J. Med. Pharm. Soc. WAKAN-YAKU 2, 124–125.

Hatano, T., Kira, R., Yoshizaki, M., Okuda, T., 1986a. Seasonal changes in the tannins of *Liquidambar formosana* reflecting their biogenesis. Phytochemistry 25, 2787–2789.

Hatano, T., Urita, K., Okuda, T., 1986b. Tannins in *Saxifraga stolonifera*. J. Med. Pharm. Soc. WAKAN-YAKU 3, 434–435.

Hatano, T., Hattori, S., Okuda, T., 1986c. Tannins of *Coriaria japonica*. I. Chem. Pharm. Bull. 34, 4092–4097.

Hatano, T., Okuda, T., Fujita, Y., Kimura, Y., Okuda, H., Arichi, S., 1987. Antoixidative effects of caffetannins from Artemisia species on arachidonate metabolism. J. Med. Pharm. Soc. WAKAN-YAKU 4, 350–351.

Hatano, T., Yoshida, T., Okuda, T., 1988a. Multiple peaks in high-performance liquid chromatography of some hydrolyzable tannins. J. Chromatogr. 435, 285–295.

Hatano, T., Kira, R., Yasuhara, T., Okuda, T., 1988b. Isorugosins A, B, and D, new ellagitannins from *Liquidambar formosana*. Chem. Pharm. Bull. 36, 3920–3927.

Hatano, T., Ogawa, N., Kira, R., Yasuhara, T., Okuda, T., 1989a. Cornusiin A, B and C, dimeric, monomeric and trimeric hydrolyzable tannins from *Cornus officinalis*, and orientation of valoneoyl group in isolated tannins. Chem. Pharm. Bull. 37, 2083–2090.

Hatano, T., Yasuhara, T., Okuda, T., 1989b. Cornusiins D, E and F, new dimeric and trimeric hydrolyzable tannins from *Cornus officinalis*. Chem. Pharm. Bull. 37, 2665–2669.

Hatano, T., Edamatsu, Hiramatsu, M., Mori, A., Fujita, Y., Yasuhara, T., Yoshida, T., Okuda, T., 1989c. Effects of tannins and related polyphenols on superoxide anion radical, and on 1,1-diphenyl-2-picrylhydrazyl radical. Chem. Pharm. Bull. 37, 2016–2021.

Hatano, T., Okonogi, A., Yazaki, K., Okuda, T., 1990a. Trapanins A and B, oligomeric hydrolyzable tannins from *Trapa japonica* Flerov. Chem. Pharm. Bull. 38, 2707–2711.

Hatano, T., Yasuhara, T., Yoshihara, R., Agata, I., Noro, T., Okuda, T., 1990b. Inhibitory effects of tannins and related polyphenols on xanthine oxidase. Chem. Pharm. Bull. 38, 1224–1229.

Hatano, T., Ogawa, N., Shingu, T., Okuda, T., 1990c. Rugosins D, E, F and G, dimeric and trimeric hydrolyzable tannins with valoneoyl group(s), from flower petals of *Rosa rugosa* Thunb.. Chem. Pharm. Bull. 38, 3341–3346.

Hatano, T., Yasuhara, T., Matsuda, M., Yazaki, K., Yoshida, T., Okuda, T., 1990d. Oenothein B, a dimeric hydrolysable tannin with macrocyclic structure, and accompanying tannins from *Oenothera erythrosepara*. J. Chem. Soc. Perkin Trans 1, 2735–2743.

Hatano, T., Yasuhara, T., Abe, R., Okuda, T., 1990e. A galloylated monoterpene glucoside and a dimeric hydrolysable tannin from *Cornus officinalis*. Phytochemistry 29, 2975–2978.

Hatano, T., Shida, S., Han, L., Okuda, T., 1991a. Camelliatannins A and B, two new complex tannins from *Camellia japonica* L. Chem. Pharm. Bull. 39, 876–880.

Hatano, T., Yasuhara, T., Yoshihara, R., Ikegami, Y., Matsuda, M., Yazaki, K., Agata, I., Nishibe, S., Noro, T., Yoshizaki, M., Okuda, T., 1991b. Inhibitory effects of galloylated flavonoids on xanthine oxidase. Planta Med. 57, 83–84.

Hatano, T., Okonogi, A., Okuda, T., 1992. Oligomeric hydrolyzable tannins from *Liquidambar formosana* and spectral analysis of the orientation of valoneoyl groups in their molecules. In: Hemingway, R.W., Laks, P.E. (Eds.), Plant polyphenols, synthesis, properties, significance. Plenum Press, New York, pp. 195–207.

Hatano, T., Han, L., Taniguchi, S., Shingu, T., Okuda, T., Yoshida, T., 1995. Camelliatannins C and E, new complex tannins from *Camellia japonica* leaves. Chem. Pharm. Bull. 43, 1629–1633.

Hatano, T., Kusuda, M., Hori, M., Shiota, S., Tsuchiya, T., Yoshida, T., 2003. Theasinensin A, a tea polyphenol formed from (−)-epigallocatechin gallate suppressed antibiotic-resistance of methicillin resistant *Staphylococcus aureus*. Planta Medica 69, 984–989.

Hayatsu, H., Inada, N., Kakutani, T., Arimoto, S., Negishi, T., Mori, K., Okuda, T., Sakata, I., 1992. Suppression of genotoxicity of carcinogens by (−)-epigallocatechin gallate. Preventive Medicine 21, 370–376.

Inoue, M., Suzuki, R., Koide, T., Sakaguchi, N., Ogihara, Y., Yabu, Y., 1994. Antioxidant, gallic acid, induces apoptosis in HL-60 RG cells. Biochem. Biophys. Commun. 204, 898–904.

Ito, H., Hatano, T., Namba, O., Shirono, T., Okuda, T., 1999a. Modified dehydrogeraniins, geraniinic acids B and C, and phyllanthusiin F. Chem. Pharm. Bull. 47, 1148–1151.

Ito, H., Miyake, M., Nishitani, E., Mori, K., Hatano, T., Okuda, T., Konoshima, T., Kozuka, M., Mukainaka, T., Tokuda, H., Nishino, H., Yoshida, T., 1999b. Anti-tumor promoting activity of polyphenols from *Cowania mexicana* and *Colegyne ramosissima*. Cancer Lett. 143, 5–13.

Iwata, S., Fukaya, Y., Nakazawa, K., Okuda, T., 1987. Effects of tannins on the oxidative damage of mouse ocular lens I. Using the oxidative damage model induced by the xanthine–xanthine oxidase system. J. Ocular Pharmacol. 3, 227–238.

Jose, H., Isaza, M., Ito, H., Yoshida, T., 2001. Tetrameric and pentameric ellagitannins from *Monochaetum multiflorum*. Heterocycles 55 (1), 29–32.

Kakiuchi, N., Hattori, M., Nishizawa, M., Yamagishi, Okuda, T., 1986. Inhibitory effect of various tannins on glucan synthesis by glucosyltransferase from *Streptococcus mutans*. Chem. Pharm. Bull. 34, 720–725.

Kanoh, R., Hatano, T., Ito, H., Yoshida, T., Akagi, M., 2000. Effects of tannins and related polyphenols on superoxide-induced histamine release from rat peritoneal mast cells. Phytomedicine 7, 297–302.

Kashiwada, Y., Nonaka, G., Nishioka, I., 1986. Rhubarb (7), Isolation and characterization of new dimeric and trimeric procyanidins. Chem. Pharm. Bull. 34, 4083–4091.

Kimura, Y., Okuda, H., Okuda, T., Yoshida, T., Hatano, T., Arichi, S., 1983. Effects of various tannins and related compounds on adrenocorticotropic hormone-induced lipolysis and insulin-induced lipogenesis from glucose in fat cells. Chem. Pharm. Bull. 31, 2501–2506.

Kimura, Y., Okuda, H., Mori, K., Okuda, T., Arichi, S., 1984a. Effects of various extracts of *Geranii herba* and geraniin on liver injury and lipid metabolism in rats fed peroxidized oil. Chem. Pharm. Bull. 32, 1866–1871.

Kimura, Y., Okuda, H., Okuda, T., Hatano, T., Agata, I., Arichi, S., 1984b. Inhibitory effects of tannins on lipid peroxidation in mitochondria and microsomes of liver. Planta Med. 50, 473–477.

Kimura, Y., Okuda, H., Okuda, T., Agata, I., Arichi, S., 1985. Inhibitory effects of caffeoylquinic acids on histamine release from rat peritoneal mast cells. Chem. Pharm. Bull. 33, 690–696.

Kimura, Y., Okuda, H., Okuda, T., Arichi, S., 1986. Effects of geraniin, corilagin and ellagic acid isolated from Geranii herba on arachidonate metabolism in leukocytes. Planta Med., 337–339.

Kimura, Y., Okuda, H., Okuda, T., Hatano, T., Arichi, S., 1987. Effects of caffetannins and related compounds on arachidonate metabolism in human polymorphonuclear leukocytes. J. Nat. Prod. 50, 392–399.

Kolodziej, H., Kayser, O., Kiderlen, A., Ito, H., Hatano, T., Yoshida, T., Foo, L.Y., 2001a. Antileishmanial activity of hydrolysable tannins and their modulatory effects on nitric oxide and tumor necrosis factor-α release in macrophages in vitro. Planta Medica 67, 825–832.

Kolodziej, H., Kayser, O., Kiderlen, A., Ito, H., Hatano, T., Yoshida, T., Foo, L.Y., 2001b. Proanthocyanidins and related compounds: Antileishmanial activities and modulatory effects on nitric oxide on tumor necrosis factor. Biol. Pharm. Bull. 24, 1016–1021.

Lee, M.-H., Nishimoto, S., Yang, L.-L., Hatano, T., Yoshida, T., Okuda, T., 1997. Two macrocyclic hydrolysable tannin dimers from *Eugenia uniflora*. Phytochemistry 44, 1343–1349.

Liu, Y., Wu, Y., Yuan, K., Ji, C., Hou, A., Yoshida, T., Okuda, T., 1997. Astragalin 2″,6″-di-*O*-gallate from *Loropetalum chinense*. Phytochemistry 46, 389–391.

Luger, P., Weber, M., Kashino, S., Amakura, Y., Yoshida, T., Okuda, T., Beurskens, G., Dauter, Z., 1998. Structure of the tannin geraniin based on conventional X-ray data at 295 K and on synchrotron data at 293 and 120 K. Acta Cryst. B54, 687–694.

Matsuo, T., Itoo, S., 1978. The chemical structure of kaki-tannin from immature fruit of the persimmon (*Diospyros kaki* L.). Agric. Biol. Chem. 42, 1637–1643.

Mayer, W., 1971. Uber die Gerbstoffe aus dem Holz der Edelkastanie und Eiche. Das Leder 22, 277–283.

Miyamoto, K., Kishi, N., Koshiura, R., Yoshida, T., Hatano, T., Okuda, T., 1987. Relationship between the structures and the antitumor activities of tannins. Chem. Pharm. Bull. 35, 814–822.

Miyamoto, K., Nomura, M., Murayama, T., Furukawa, T., Hatano, T., Yoshida, T., Koshiura, R., Okuda, T., 1993a. Antitumor activities of ellagitannins against Sarcoma-180 in mice. Biol. Pharm. Bull. 16, 379–387.

Miyamoto, K., Murayama, T., Nomura, M., Hatano, T., Yoshida, T., Furukawa, T., Koshiura, R., Okuda, T., 1993b. Antitumor activity and interleukin-1 induction by tannins. Anticancer Res. 13, 37–42.

Miyamoto, K., Nomura, M., Sasakura, M., Matsui, E., Koshiura, R., Murayama, T., Furukawa, T., Hatano, T., Yoshida, T., Okuda, T., 1993c. Antitumor activity of oenothein B, a unique macrocyclic ellagitannin. Jpn. J. Cancer Res. 84, 99–103.

Miyamoto, K., Murayama, T., Yoshida, T., Hatano, T., Okuda, T., 1997. Anticarcinogenic activities of polyphenols in foods and herbs. In: Shahidi, F. (Ed.), Antinutrients and phytochemicals in food. Amer. Chem. Soc., Washington, DC, pp. 245–259.

Nakanishi, Y., Qu, L., Oda, M., Okuda, T., Abe, H., 1991. Effect of geraniin on the ulcer induced by hydrochloric acid-ethanol. J. Med. Pharm. Soc. WAKAN-YAKU 8, 330–331.

Nakanishi, Y., Orita, M., Okuda, T., Abe, H., 1998a. Effects of geraniin on the liver in rat. I. Effects of geraniin compared to ellagic acid on hepatic injuries induced by CCl_4 D-galactpsamine, and thioacetamide. Nat. Med. 52, 396–403.

Nakanishi, Y., Kubo, M., Okuda, T., Abe, H., 1998b. Effects of geraniin on the liver in rats. II. Liver drug-metabolizing enzymes. Nat. Med. 52, 404–408.

Nakanishi, Y., Okuda, T., Abe, H., 1999a. Effects of geraniin on the liver in rats. III. Correlation between lipid accumulations and liver damage in CCl_4-treated rats. Nat. Med. 53, 22–26.

Nakanishi, Y., Kubo, M., Okuda, T., Abe, H., 1999b. Effect of geraniin on aminonucleoside nephrosis in rats. Nat. Med. 53, 94–100.

Nakashima, H., Murakami, T., Yamamoto, N., Sakagami, S., Tanuma, T., Hatano, T., Yoshida, T., Okuda, T., 1992. Inhibition of human immunodeficiency viral replication by tannins and related compounds. Antiviral Res. 18, 91–103.

Okabe, S., Suganuma, M., Hayashi, M., Sueoka, E., Komori, A., Fujiki, H., 1997. Mechanism of growth inhibition of human lung cancer cell line, PC-9, by tea polyphenols. Jpn. J. Cancer Res. 88, 639–643.

Okabe, S., Suganuma, M., Imayoshi, Y., Taniguchi, S., Yoshida, T., Fujiki, H., 2001. TNF-α releasing inhibitors, geraniin and corilagin, in leaves of *Acer nikoense*, Megusurino-ki. Biol. Pharm. Bull. 24, 1145–1148.

Okuda, T., 1978. A tannin lacking astringent taste. Farumashia 14, 653–656.

Okuda, T., 1997. Structure–activity relationship of antioxidant and antitumor polyphenols. In: Ohigashi, H., Osawa, T., Terao, J., Watanabe, S., Yoshikawa, T. (Eds.), Food factors for cancer prevention. Springer-Verlag, Tokyo, pp. 280–285.

Okuda, T., 1998. Correlation of tannin structures with plant taxonomy and antitumor and antioxidant activities. In: Ageta, H., Aimi, N., Ebizuka, Y., Fujita, T., Honda, G. (Eds.), Towards natural medicine research in the 21st century. Elsevier, Amsterdam, pp. 15–26.

Okuda, T., 1999a. Novel aspects of tannins – Renewed concepts and structure–activity relationships. Curr. Org. Chem. 3, 609–622.

Okuda, T., 1999b. Antioxidants in herbs: Polyphenols. In: Packer, L., Hiramatsu, M., Yoshikawa, T. (Eds.), Antioxidant food supplements in human health. Academic Press, San Diego, pp. 393–410.

Okuda, T., 1999c. *Geranium thunbergii*, a notable Japanese folk medicine, led to recent tannin research development. Nat. Med. 53, 52–54.

Okuda, T., Seno, K., 1981. Tannins in the leaf of *Mallotus japonicus*. J. Chem. Soc. Jpn., 671–677.

Okuda, T., Yoshida, T., 1980. ^{13}C Nuclear magnetic resonance spectra of corilagin and geraniin. Heterocycles 14, 1743–1749.

Okuda, T., Yoshida, T., Mori, K., 1975. Studies on the constituents of *Geranium thunbergii* II. Yakugaku Zasshi 95, 1462–1466.

Okuda, T., Mori, K., Aoi, K., 1977a. Difference of tannin activity by structural differences. Effects of pH variation to relative astringency. Yakugaku Zasshi 97, 1267–1272.

Okuda, T., Yoshida, T., Nayeshiro, H., 1977b. Structure of geraniin. Chem. Pharm. Bull. 25, 1862–1869.

Okuda, T., Mori, K., Ishino, M., 1979. Transformations of geraniin upon decoction. Yakugaku Zasshi 99, 505–509.

Okuda, T., Mori, K., Hatano, T., 1980a. The distribution of geraniin and mallotusinic acid in the order Geraniales. Phytochemistry 19, 547–551.

Okuda, T., Yoshida, T., Hatano, T., 1980b. Equilibrated stereostructures of hydrated geraniin and mallotusinic acid. Tetrahedron Lett., 2561–2564.

Okuda, T., Hatano, T., Nitta, H., Fujii, R., 1980c. Hydrolyzable tannins having enantiomeric dehydrohexahydroxydiphenoyl group: Revised structure of terchebin and structure of granatin B. Tetrahedron Lett., 4361–4364.

Okuda, T., Hatano, T., Yasui, T., 1981a. Revised structure of isoterchebin, isolated from *Cornus officinalis*. Heterocycles 16, 1321–1324.

Okuda, T., Yoshida, T., Ashida, M., 1981b. Casuarictin and casuarinin, two new ellagitannins from *Casuarina stricta*. Heterocycles 16, 1681–1685.

Okuda, T., Yoshida, T., Mori, K., Hatano, T., 1981c. Tannins in medicinal plants and drugs. Heterocycles 15, 1323–1348.

Okuda, T., Yoshida, T., Hatano, T., 1982a. Hydrated stereostructure and equilibration of geraniin. J. Chem. Soc. Perkin Trans. 1, 9–14.

Okuda, T., Hatano, T., Yazaki, K., 1982b. Dehydrogeraniin, furosinin and furosin, dehydroellagitannins from *Geranium thunbergii*. Chem. Pharm. Bull. 30, 1113–1116.

Okuda, T., Yoshida, T., Hatano, T., Koga, T., Toh, N., Kuriyama, K., 1982c. Circular dichroism of hydrolysable tannins. I. Ellagitannins and gallotannins. Tetrahedron Lett. 23, 3937–3940.

Okuda, T., Yoshida, T., Hatano, T., Koga, T., Toh, N., Kuriyama, K., 1982d. Circular dichroism of hydrolysable tannins. II. Dehydroellagitannins. Tetrahedron Lett. 23, 3941–3944.

Okuda, T., Yoshida, T., Kuwahara, M., Memon, M.U., Shingu, T., 1982e. Agrimoniin and potentillin, an ellagitannin dimer and monomer having an α-glucose core. J. Chem. Soc., Chem. Commun., 163–164.

Okuda, T., Yoshida, T., Ashida, M., Yazaki, K., 1982f. Casuariin, stachyurin and strictinin, new ellagitannins from *Casuarina stricta* and *Stachyurus praecox*. Chem. Pharm. Bull. 30, 766–769.

Okuda, T., Yoshida, T., Hatano, T., Yazaki, K., Ashida, M., 1982g. Ellagitannins of the Casuarinaceae, Stachyuraceae and Myrtaceae. Phytochemistry 21, 2871–2874.

Okuda, T., Mori, K., Shiota, M., Ida, K., 1982h. Reduction of heavy metal ions and solubilization of precipitates by tannins. Yakugaku Zasshi 102, 735–742.

Okuda, T., Yoshida, T., Ashida, M., Yazaki, K., 1983a. Structures of pedunculagin, casuarictin, strictinin, casuarinin, and stachyurin. J. Chem. Soc. Perkin Trans. 1, 1765–1772.

Okuda, T., Kimura, Y., Yoshida, T., Hatano, T., Okuda, H., Arichi, S., 1983b. Inhibitory effects of tannins on lipid peroxidation in mitochondria and microsomes of liver. Chem. Pharm. Bull. 31, 1625–1631.

Okuda, T., Mori, K., Hayatsu, H., 1984a. Inhibitory effect of tannins on direct-acting mutagens. Chem. Pharm. Bull. 32, 3755–3758.

Okuda, T., Yoshida, T., Kuwahara, M., Memon, M.U., Shingu, T., 1984b. Structures of potentillin, agrimonic acids A and B, and agrimoniin, a dimeric ellagitannin. Chem. Pharm. Bull. 32, 2165–2173.

Okuda, T., Hatano, T., Yazaki, K., 1984c. Guavin B, an ellagitannin of novel type. Chem. Pharm. Bull. 32, 3787–3788.

Okuda, T., Hatano, T., Ogawa, N., Kira, R., Matsuda, M., 1984d. Cornusiin A, a dimeric ellagitannin forming four tautomers, and accompanying new tannins in *Cornus officinalis*. Chem. Pharm. Bull. 32, 4662–4665.

Okuda, T., Mori, K., Hatano, T., 1985. Relationship of the structures of tannins to the binding activities with hemoglobin and methylene blue. Chem. Pharm. Bull. 33, 1424–1433.

Okuda, T., Yoshida, T., Hatano, T., Ikeda, Y., Shingu, T., Inoue, T., 1986a. Isolation of water-soluble tannins by centrifugal partition chromatography, and biomimetic synthesis of elaeocarpusin. Chem. Pharm. Bull. 34, 4075–4082.

Okuda, T., Yoshida, T., Hatano, T., Yazaki, K., Kira, R., Ikeda, Y., 1986b. Preparative fractionation of hydrolysable tannins by centrifugal partition chromatography. J. Chromatogr. 362, 375–381.

Okuda, T., Hatano, T., Agata, I., Nishibe, S., 1986c. Rosmarinic acid from labiate plants in Japan. Yakugaku Zasshi 106, 1108–1111.

Okuda, T., Hatano, T., Agata, I., Nishibe, S., Kimura, K., 1986d. Tannins in *Artemisia montana*, *A princeps* and related plant species. Yakugaku Zasshi 106, 894–899.

Okuda, T., Yoshida, T., Hatano, T., Yazaki, K., Ikegami, Y., Shingu, T., 1987a. Guavins A, C and D, complex tannins from *Psidium guajava*. Chem. Pharm. Bull. 35, 443–446.

Okuda, T., Hatano, T., Kaneda, T., Yoshizaki, M., Shingu, T., 1987b. Liquidambin, an ellagitannin from *Liquidambar formosana*. Phytochemistry 26, 2053–2055.

Okuda, T., Yoshida, T., Hatano, T., 1989. New methods of analyzing tannins. J. Nat. Prod. 52, 1–31.

Okuda, T., Yoshida, T., Hatano, T., 1991. Chemistry and biological activities of tannins in medicinal plants. In: Wagner, H., Farnsworth, N.R. (Eds.), Economic and medicinal plants research, vol. 5. Academic Press, New York, pp. 129–165.

Okuda, T., Yoshida, T., Hatano, T., 1992a. Polyphenols from Asian plants - – Structural diversity, and antitumor and antiviral activities. In: Huang, M.-T., Ho, C.-T., Lee, C.Y. (Eds.), Phenolic compounds in food and their effects on health II, ACS Symposium Series, vol. 507, pp. 160–183.

Okuda, T., Yoshida, T., Hatano, T., 1992b. Pharmacologically active tannins isolated from medicinal plants. In: Hemingway, R.W., Laks, P.E. (Eds.), Plant polyphenols: biogenesis, chemical properties and significance. Plenum Press, New York, pp. 539–569.

Okuda, T., Yoshida, T., Hatano, T., Kubo, M., Orime, T., Yoshizaki, M., Naruhashi, N., 1992c. Hydrolysable tannins as chemotaxonomic markers in the Rosaceae. Phytochemistry 31, 3091–3096.

Okuda, T., Yoshida, T., Hatano, T., 1993a. Classification of oligomeric hydrolysable tannins and specificity of their occurrence in plants. Phytochemistry 32, 507–521.

Okuda, T., 1993b. Natural polyphenols as antioxidants and their potential use in cancer prevention. In: Scalbert, A. (Ed.), Polyphenolic phenomena. INRA, Paris, pp. 221–235.

Okuda, T., Yoshida, T., Hatano, T., 1995. Hydrolyzable tannins and related polyphenols. In: Herz, W., Kirby, G.W., Moore, R.E., Steglich, W., Tamm, C. (Eds.), Progress in the chemistry of organic natural products, vol. 66. Springer-Verlag, Wien, New York.

Okuda, T., Yoshida, T., Hatano, T., 2000. Correlation of oxidative transformation of hydrolysable tannins and plant evolution. Phytochemistry 55, 513–529.

Sakagami, H., Hatano, T., Yoshida, T., Tanuma, S., Hata, N., Misawa, Y., Ishii, N., Tsutsumi, T., Okuda, T., 1990. Stimulation of granulocytic cell iodination by tannins and related compounds. Anticancer Res. 10, 1523–1532.

Sakagami, H., Asano, K., Tanuma, S., Hatano, T., Yoshida, T., Okuda, T., 1992. Stimulation of monocyte iodination and IL-1 production by tannins and related compounds. Anticancer Res. 12, 377–388.

Sakagami, H., Kuribayashi, N., Iida, M., Sakagami, T., Takeda, M., Fukuchi, K., Gomi, K., Ohata, H., Momose, K., Kawazoe, Y., Hatano, T., Yoshida, T., Okuda, T., 1995. Induction of DNA fragmentation by tannin- and lignin-related substances. Anticancer Res. 15, 2121–2128.

Sakagami, H., Satoh, K., Hatano, T., Yoshida, T., Okuda, T., 1997. Possible role of radical intensity and oxidation potential for gallic acid-induced apoptosis. Anticancer Res. 17, 377–380.

Sakagami, H., Satoh, K., Ida, Y., Koyama, N., Premanathan, M., Arakaki, R., Nakashima, H., Hatano, T., Okuda, T., Yoshida, T., 1999. Induction of apoptosis and anti-HIV activity by tannins- and lignin-related substances. In: Gross, G.G., Hemingway, R.W., Yoshida, T. (Eds.), Plant polyphenols 2: chemistry, biology, pharmacology, ecology. Kluwer Academic/Plenum Publishers, New York, pp. 595–611.

Satomi, H., Umemura, K., Ueno, A., Hatano, T., Okuda, T., Noro, T., 1993. Carbonic anhydrase inhibitors from the pericarps of *Punica granatum* L. Biol. Pharm. Bull. 16, 787–790.

Schmidt, O.T., 1956. Gallotannine und Ellagen-gerbstoffe. In: Zechmeister, L. (Ed.), Fortschr. Chem. Org. Naturstoffe, vol. 13. Springer, Wien, pp. 70–136.

Shimizu, M., Shiota, S., Mizushima, T., Ito, H., Hatano, T., Yoshida, T., Tsuchiya, T., 2001. Marked potentiation of activity of β-lactam against methicillin-resistant *Staphylococcus aureus* by corilagin. Antimicrob. Agents Chem. 45, 3198–3201.

Shiota, S., Shimizu, M., Mizushima, T., Ito, H., Hatano, T., Yoshida, T., Tsuchiya, T., 1999. Marked reduction in the minimum inhibitive concentration (MIC) of β-lactams in methicillin-resistant *Staphyllococcus aureus* produced by (−)-epicatechin gallate. Biol. Pharm. Bull. 22, 1388–1390.

Shiota, S., Shimizu, M., Mizushima, T., Ito, H., Hatano, T., Yoshida, T., Tsuchiya, T., 2000. Restoration of effectiveness of β-lactams in methicillin-resitant *Staphylococcus aureus* by tellimagrandin I from Rose Red. FEMS Microbiol. Lett. 185, 135–138.

Suganuma, M., Okabe, S., Oniyama, M., Tada, Y., Ito, H., Fujiki, H., 1998. Wide distribution of 3H-(−)-eligallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. Carcinogenesis 19, 1771–1776.

Tsai, Y.-J., Abe, H., Maruta, H., Hatano, T., Nishibe, H., Sakagami, H., Okuda, T., Tanuma, S., 1991. Effect of chemically defined tannins on poly(ADP-ribose) glycohydrolase activity. Biochem. Int. 24, 889–897.

Tsai, Y.-J., Aoki, T., Maruta, H., Abe, H., Sakagami, H., Hatano, T., Okuda, T., Tanuma, S., 1992. Mouse mammary tumor virus gene expression is suppressed by oligomeric ellagitannins, novel inhibitors of poly(ADP-ribose) glycohydrolase. J. Biol. Chem. 267, 14436–14442.

Yazaki, K., Okuda, T., 1989. Gallotannin production in cell cultures of *Cornus officinalis* Sieb. et Zucc. Plant Cell Report 8, 346–349.

Yazaki, K., Okuda, T., 1990. Ellagitannin formation in callus cultures of *Heterocentron roseum*. Phytochemistry 29, 1127–1130.

Yazaki, K., Shida, S., Okuda, T., 1989. Galloylhomoarbutin and related polyphenols from *Pyrola incarnata*. Phytochemistry 28, 607–609.

Yazaki, K., Yoshida, T., Okuda, T., 1991. Tannin production in cell suspension cultures of *Geranium thunbergii*. Phytochemistry 30, 501–503.

Yoshida, T., Fujii, R., Okuda, T., 1980. Revised structures of chebulinic acid and chebulagic acid. Chem. Pharm. Bull. 28, 3713–3715.

Yoshida, T., Okuda, T., Koga, T., Toh, N., 1982a. Absolute configurations of chebulic, chebulinic and chebulagic acid. Chem. Pharm. Bull. 30, 2655–2658.

Yoshida, T., Okuda, T., Memon, M.U., Shingu, T., 1982b. Structure of gemin A, a new dimeric ellagitannin having α- and β-glucose cores. J. Chem. Soc. Chem. Commun., 351–353.

Yoshida, T., Seno, K., Takama, Y., Okuda, T., 1982c. Bergenin derivatives from *Mallotus japonicus*. Phytochemistry 21, 1180–1182.

Yoshida, T., Maruyama, Y., Okuda, T., Memon, M.U., Shingu, T., 1982d. Gemins B and C, dimeric ellagitannins from *Geum japonicum*. Chem. Pharm. Bull. 30, 4245–4248.

Yoshida, T., Okuda, T., Memon, M.U., Shingu, T., 1985a. Gemins A, B, and C, new dimeric ellagitannins from *Geum japonicum*. J. Chem. Soc. Perkin Trans. 1, 315–321.

Yoshida, T., Maruyama, Y., Memon, M.U., Shingu, T., Okuda, T., 1985b. Gemins D, E, F, ellagitannins from *Geum japonicum*. Phytochemistry 24, 1041–1046.

Yoshida, T., Haba, K., Shingu, T., Okuda, T., 1987. Revised structure of nobotanin B, a dimeric ellagitannin of *Tibouchina semidecandra*. Heterocycles 26, 2845–2848.

Yoshida, T., Chen, L., Shingu, T., Okuda, T., 1988. Euphorbins A and B, novel dimeric dehydroellagitannins from *Euphorbia hirta* L. Chem. Pharm. Bull. 36, 2940–2949.

Yoshida, T., Chou, T., Haba, K., Okano, Y., Shingu, T., Miyamoto, K., Koshiura, R., Okuda, T., 1989a. Camelliin B and nobotanin I, macrocyclic ellagitannin dimers and related dimers, and their antitumor activity. Chem. Pharm. Bull. 37, 3174–3176.

Yoshida, T., Mori, K., Hatano, T., Okumura, T., Uehara, I., Komagoe, K., Fujita, Y., Okuda, T., 1989b. Radical-scavenging effects of tannins and related polyphenols on 1,1-diphenyl-2-picrylhydrazyl radical. Chem. Pharm. Bull. 37, 1919–1921.

Yoshida, T., Hatano, T., Okuda, T., 1989c. Separation of labile oligomeric hydrolysable tannins and related polyphenols by centrifugal partition chromatography. J. Chromatogr. 467, 139–147.

Yoshida, T., Chou, T., Nitta, A., Miyamoto, K., Koshiura, R., Okuda, T., 1990a. Woodfordin C, a macro-ring hydrolysable tannin dimer with antitumor activity, and accompanying dimers from *Woodfordia fruticosa* flowers. Chem. Pharm. Bull. 38, 1211–1217.

Yoshida, T., Chou, T., Maruyama, Y., Okuda, T., 1990b. Camelliins A and B, two new dimeric hydrolysable tannins from flower buds of *Camellia japonica* L. and *Camellia sasanqua* Thunb.. Chem. Pharm. Bull. 38, 2681–2686.

Yoshida, T., Namba, O., Chen, L., Okuda, T., 1990c. Euphorbin E, a hydrolyzable tannin dimer of highly oxidized structure from *Euphorbia hirta*. Chem. Pharm. Bull. 38, 1113–1115.

Yoshida, T., Chou, T., Matsuda, M., Yasuhara, T., Yazaki, K., Hatano, T., Nitta, A., Okuda, T., 1991a. Woodfordin D and oenothein A, trimeric hydrolyzable tannins of macro-ring structure with antitumor activity. Chem. Pharm. Bull. 39, 1157–1162.

Yoshida, T., Yokoyama, K., Namba, O., Okuda, T., 1991b. Tirucallins A, B and euphorbin F, monomeric and dimeric ellagitannins from *Euphorbia tirucalli* L.Chem. Pharm. Bull 39, 1137–1143.

Yoshida, T., Hatano, T., Ahmed, A.F., Okonogi, A., Okuda, T., 1991c. Structures of isorugosin E and hirtellin B, dimeric hydrolysable tannins having a trisgalloyl group. Tetrahedron 47, 3575–3584.

Yoshida, T., Ahmed, A.F., Memon, A.M., Okuda, T., 1991d. New monomeric and dimeric hydrolyzable tannins from *Roaumuria hirtella* and *Tamarix pakistanica*. Chem. Pharm. Bull. 39, 2849–2854.

Yoshida, T., Ito, H., Matsunaga, H., Tanaka, R., Okuda, T., 1992a. Hydrolyzable tannins with [$^1C_4$]-glucose core from *Phyllanthus flexusus* Muell. Arg. Chem. Pharm. Bull. 40, 53–60.

Yoshida, T., Nakata, F., Hosotani, K., Nitta, A., Okuda, T., 1992b. Three new complex tannins from *Melastoma malabathricum* L. Chem. Pharm. Bull. 40, 1727–1732.

Yoshida, T., Nakata, K., Hosotani, K., Nitta, A., Okuda, T., 1992c. Dimeric hydrolysable tannins from *Melastoma malabathricum*. Phytochemistry 31, 2829–2833.

Yoshida, T., Chou, T., Nitta, A., Okuda, T., 1992d. Hydrolyzable tannin oligomers with macrocyclic structures, and accompanying tannins from *Woodfordia fruticosa* Kurz. Chem. Pharm. Bull. 40, 2023–2030.

Yoshida, T., Ahmend, A.F., Memon, M.U., Okuda, T., 1993. Dimeric hydrolysable tannins from *Tamarix pakistanica*. Phytochemistry 33, 197–202.

Yoshida, T., Hatano, T., Ito, H., Okuda, T., 1999. Highly oxidized ellagitannins and their biological activity. In: Gross, G.G., Hemingway, R.W., Yoshida, T. (Eds.), Plant polyphenols, vol. 2. Kluwer/Academic/Plenum Publishers, New York, pp. 127–144.

Yoshida, T., Hatano, T., Ito, H., Okuda, T., 2000. Chemical and biological perspectives of ellagitannin oligomers from medicinal plants. In: Atta-ur-Rahman (Ed.), Studies in natural products chemistry, vol. 23. Elsevier Science B.V., Amsterdam, pp. 395–453.

Yoshizawa, S., Horiuchi, T., Fujiki, H., Yoshida, T., Okuda, T., Sugimura, T., 1987. Antitumor promoting activity of (−)-epigallocatechin gallate, the main constituent of "tannin" in green tea. Phytotherapy Res. 1, 44–47.

Yoshizawa, S., Horiuchi, T., Suganuma, M., Nishiwaki, S., Yatsunami, J., Okabe, S., Okuda, T., Muto, Y., Frenkel, K., Troll, W., Fujiki, H., 1992. Penta-O-galloyl-β-D-glucose and (−)-epigallocatechin gallate: Cancer preventive agents. In: Ho, C.-T., Lee, C.-Y., Huang, M.-T. (Eds.), Phenolic compounds in food and their effects on health II, ACS Symposium Series, vol. 507, pp. 380–387.

Professor Takuo Okuda was born in 1927 in Nara, Japan, and obtained his doctorate degree in Pharmaceutical Sciences in 1955 from Kyoto University. In 1962 he was an Associate Professor at Kyoto University, and then from 1970 to 1993, became Professor of Pharmacognosy at the newly founded Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama, where he started his research of tannins in medicinal plants. He is now an Emeritus Professor of this university, and was also a visiting professor at the Stevens Institute of Technology, NJ, USA in 1983, and the Taipei Medical University, Taipei, Taiwan, from 1993 to 1994. He has published about 320 original research papers in refereed journals, 50 reviews in scientific journals and 60 chapters in books, and was an editor of six books of pharmacognosy (natural product chemistry) and medicinal plants. Prof. Okuda was President of the Japanese Society of Pharmacognosy from 1995 to 1996, and is an honored member of this Society, and also of the Japanese Society for Food Factors. He is an Emeritus Member of the American Society of Pharmacognosy. He was on various editorial boards such as Phytochemistry from 1994 to 2000, and Chem. Pharm. Bull. from 1984 to 1985, as much as is an editorial adviser of Natural Product Research, Letters in Organic Chemistry, Mini-reviews in Organic Chemistry and Research Advances in Phytochemistry. He has been organizer or general secretary in various domestic and international symposia and meetings, such as the XV International Botanical Congress (Tokyo) and the International Congress on Natural Product Research (Park City, USA).