

#### IV. 研究成果の刊行物・別刷

Review

## Structural Features and Biological Properties of Ellagitannins in Some Plant Families of the Order Myrtales

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**Abstract:** Plant tannins, including hydrolysable and condensed varieties, are well known antioxidants in medicinal plants, foods, and edible fruits. Their diverse biological properties and potential for disease prevention have been demonstrated by various *in vitro* and *in vivo* assays. A number of ellagitannins, the largest group of hydrolysable tannins, have been isolated from dicotyledonous angiosperms and characterized. This diverse class of tannins is sub-grouped into simple ellagitannins, C-glycosidic ellagitannins, complex tannins (condensates of C-glycosidic tannins with flavan-3-ol), and oligomers up to pentamers. This review outlines and describes the chemotaxonomic significance of structural features in various types of ellagitannins found in plants belonging to the Myrtaceae, Onagraceae, and Melastomataceae families, which are all included in the order Myrtales. Any biological activities that have been reported, including antitumor and antibacterial effects as well as enzyme inhibition, are also reviewed.

**Keywords:** ellagitannins; C-glycosidic ellagitannins; oligomeric ellagitannins; Myrtales; biological activity

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## 1. Introduction

Plant tannins, one of the major groups of antioxidant polyphenols found in food and beverages, have attracted a lot of attention in recent years because of their multifunctional properties beneficial to human health. These diverse tannins may be divided into two large groups: condensed and hydrolysable. Condensed tannins are formed through the condensation of flavan-3-ols (catechins) and are often referred to as proanthocyanidins. Among the more than 500 hydrolysable tannins hitherto characterized, ellagitannins, which produce ellagic acid upon hydrolysis, constitute the largest group; the remaining group is gallotannins (galloylglucoses). The ellagitannins include: (1) monomeric ellagitannins, (2) *C*-glycosidic ellagitannins with an open-chain glucose core, (3) condensates of *C*-glycosidic tannins with flavan-3-ol (complex tannin), and (4) oligomers which are produced through intermolecular C-O or C-C bonds between monomers [1,2]. Unlike the condensed tannins that are widespread throughout the plant kingdom, ellagitannins have been found only in dicotyledonous angiosperms. Among the plant families rich in ellagitannins are the Myrtaceae, Lythraceae, Onagraceae, Melastomataceae, and Combretaceae [3]. These families belong to the order Myrtales according to the plant classification systems of New Engler, Cronquist, and APGII (angiosperm phylogeny group) [4]. Ellagitannins have also been isolated from plant species of Trapaceae and Punicaceae, which belong to Myrtales in Cronquist's and the New Engler's systems. This review outlines and describes the chemotaxonomic significance of structural features found in various types of ellagitannins, focusing on representative examples found in the plants of Myrtales. Any observed antioxidative and antitumor effects of these ellagitannins are also reviewed.

## 2. Monomeric Ellagitannins

### 2.1. Simple Ellagitannins

Ellagitannins are characterized by the presence of one or more hexahydroxydiphenoyl (HHDP) unit(s) on a glucopyranose core. The HHDP group is biosynthetically formed through intramolecular, oxidative C-C bond formation between neighboring galloyl groups in galloylglucoses [5]. They are easily hydrolysed, either enzymatically or with acid, to liberate a stable ellagic acid as the dilactone form of hexahydroxydiphenic acid. In addition to the HHDP group, other constituent acyl units in ellagitannins include a galloyl group and HHDP metabolites such as valoneoyl, dehydrohexahydroxydiphenoyl (DHHDP), and chebuloyl groups. Variations in the number and position of these acyl units on the glucose core provide a variety of analogs such as tellimagrandin I (1), and II (2), pedunculagin (6), casuarictin (7) [6], chebulagic acid (14), and chebulinic acid (15) [7] (Figure 1). Note that the chiral HHDP group at O-2/O-3 and O-4/O-6 of the glucose residue has an *S*-configuration, whereas that at O-3/O-6 has an *R*-configuration, as indicated by a positive and negative Cotton effect around 230 nm in their respective circular dichroism (CD) spectra [8].

Representative ellagitannin monomers thus far isolated from the Myrtaceae, Melastomataceae, Onagraceae, Trapaceae, Combretaceae, and Punicaceae families are summarized in Figure 1 and Table 1.

Figure 1. Structures of monomeric ellagitannins 1–15.

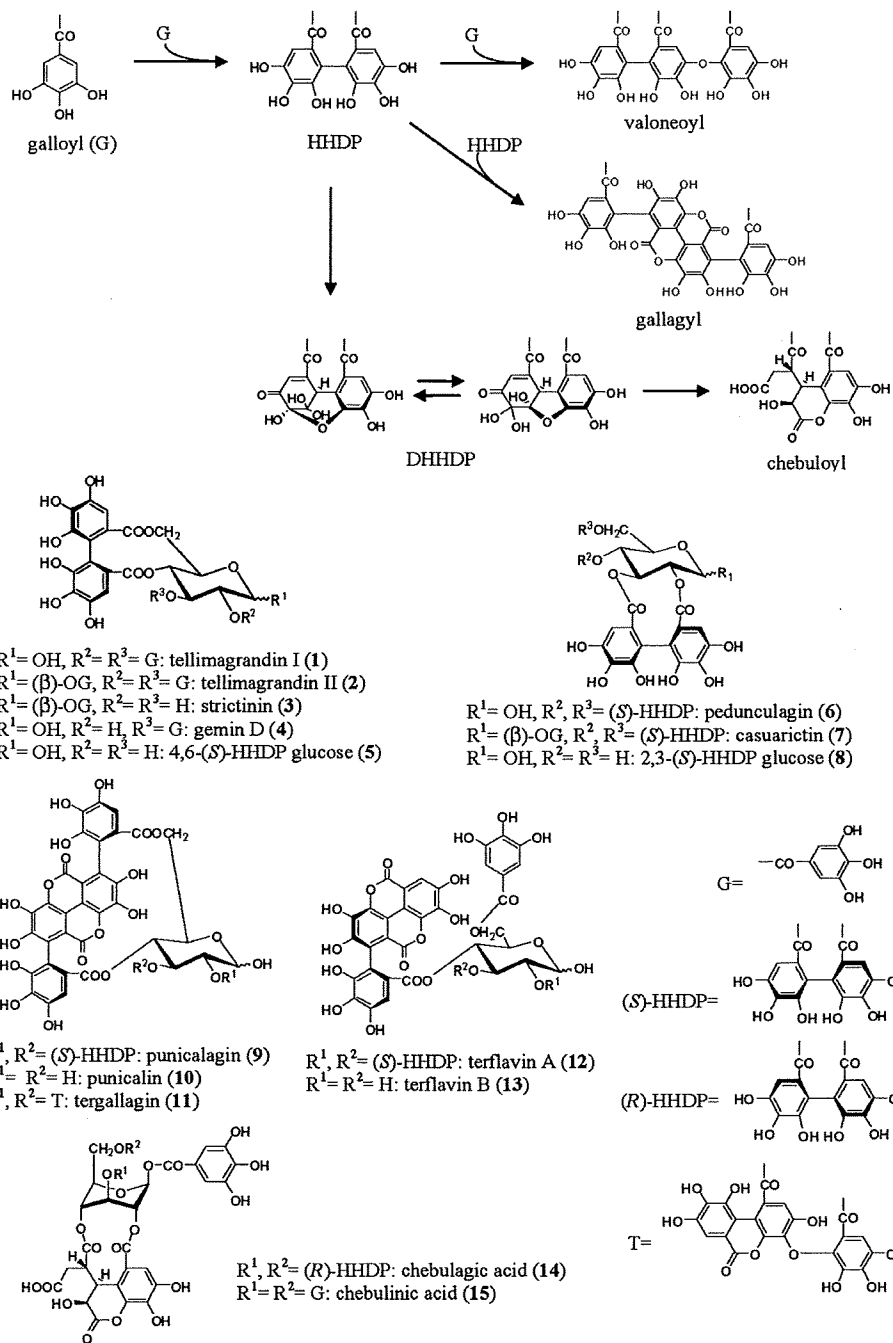


Table 1. Ellagitannin monomers found in the Myrtales.

Tannin	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
<b>Plant source [Ref]</b>															
Trapaceae															
<i>Trapa japonica</i> [9]	+			+		+	+								
Melastomataceae															
<i>Bredia tuberculata</i> [10]						+	+								
<i>Heterocentron roseum</i> [11]			+					+							
<i>Melastoma malabathricum</i> [12]			+				+	+							
<i>M. normale</i> [10]			+				+	+							
<i>Tibouchina semidecandra</i> [13]						+	+	+							
Myrtaceae															
<i>Callistemon lanceolatus</i> [14]				+		+		+							
<i>Eucalyptus alba</i> [15]	+			+		+		+							
<i>E. considiana</i> [16]	+		+	+		+									
<i>E. globulus</i> [17]	+														
<i>E. rostrata</i> [18]	+														
<i>E. viminalis</i> [16]	+	+		+		+									
<i>Myrtus communis</i> [19]	+	+													
<i>Pimenta dioica</i> [20]		+	+		+	+									
<i>Syzygium aqueum</i> [21]		+				+	+								
<i>S. aromaticum</i> [22]	+	+	+	+			+								
Onagraceae															
<i>Epilobium angustifolium</i> [23]	+		+	+		+									
<i>Oenothera erythrosepala</i> [24]	+			+											
<i>O. laciniata</i> [25]	+														
<i>O. tetraptera</i> [26]	+	+		+											
Combretaceae															
<i>Combretum glutinosum</i> [27]								+	+	+					
<i>C. molle</i> [28]										+	+				
<i>Quisqualis indica</i> [29]	+	+				+		+	+	+					
<i>Terminalia arborea</i> [30]								+	+	+				+	+
<i>T. arjuna</i> [31]								+	+	+					
<i>T. brachystemma</i> [32]									+						
<i>T. calamansanai</i> [33]	+	+						+	+	+					
<i>T. catappa</i> [34]	+							+	+	+	+	+	+	+	+
<i>T. chebula</i> [35]									+	+		+	+	+	+
<i>T. citrina</i> [36]									+					+	
<i>T. macroptera</i> [37]								+	+			+	+		
<i>T. myriocarpa</i> [38]								+	+						
<i>T. triflora</i> [39]											+				
Punicaceae															
<i>Punica granatum</i> [40]	+		+			+		+	+	+					

Ellagitannins having a  $^4C_1$ -glucopyranose core, e.g., 1–8, have been isolated along with gallotannins from various other plant families and show little chemotaxonomic significance. The considerably rare tannins punicalagin (9) and punicalin (10), both of which contain a gallagyl unit and were first isolated from the pericarps of pomegranate (*Punica granatum* Punicaceae) [40], were a characteristic component in some *Terminalia* species. This supports the hypothesis that Punicaceae is chemotaxonomically proximate to Combretaceae as classified by Cronquist and Engler. The punicalagin analogs tergalagin (11) and terflavins A (12) and B (13) were also isolated from *T. chebula* [35] and *T. catappa* [34].

Some *Terminalia* species produce ellagitannins with a  $^1C_4$ -glucopyranose core and a unique chebuloyl group, such as chebulagic acid (14) and chebulinic acid (15). Although 14 and 15 have also been found in plants of the *Geranium* [41] and *Euphorbia* genera [42], their co-occurrence with 9 and/or 10 is a chemotaxonomic feature of *Terminalia*.

## 2.2. C-Glycosidic Ellagitannins

C-Glycosidic ellagitannins have been found in many plant families, including Lythraceae, Myrtaceae, Combretaceae, Melastomataceae, and Punicaceae, as well as Fagaceae, Betulaceae, Casuarinaceae, Rosaceae, Theaceae, and Elaeagnaceae [1]. They are categorized into two types: castalagin-type, which contain a flavogalloyl unit participating in the C-glycosidic linkage, such as castalagin (16) and its C-1 epimer, vescalagin (18), and casuarinin-type, which contain an HHDP unit, such as casuarinin (20) and stachyurin (21). In addition to these tannins, their metabolites, *i.e.*, grandinin (19), casuariin (22), and 5-desgalloylstachyurin (23), have been isolated from various plants of the Myrtales (Figure 2). *Lagerstroemia flos-reginea* and *L. speciosa* (Banaba) belonging to the family Lythraceae are particularly rich in C-glycosidic tannins including 16, 18, and 20–23 and casuarinin-type metabolites including punicacortein A (24) and lagerstroemin (29). Punicacortein A (24) and its analogs epi-punicacortein A (25) and punicacortein B (26)–D (28) were isolated from *Punica granatum*. Tannins 27 and 28, which both contain a gallagyl unit, were obtained together with punicalagin (9) from *Terminalia arborea* and *T. macroptera*, respectively.

The plant sources of C-glycosidic ellagitannins obtained from the order Myrtales are listed in Table 2.

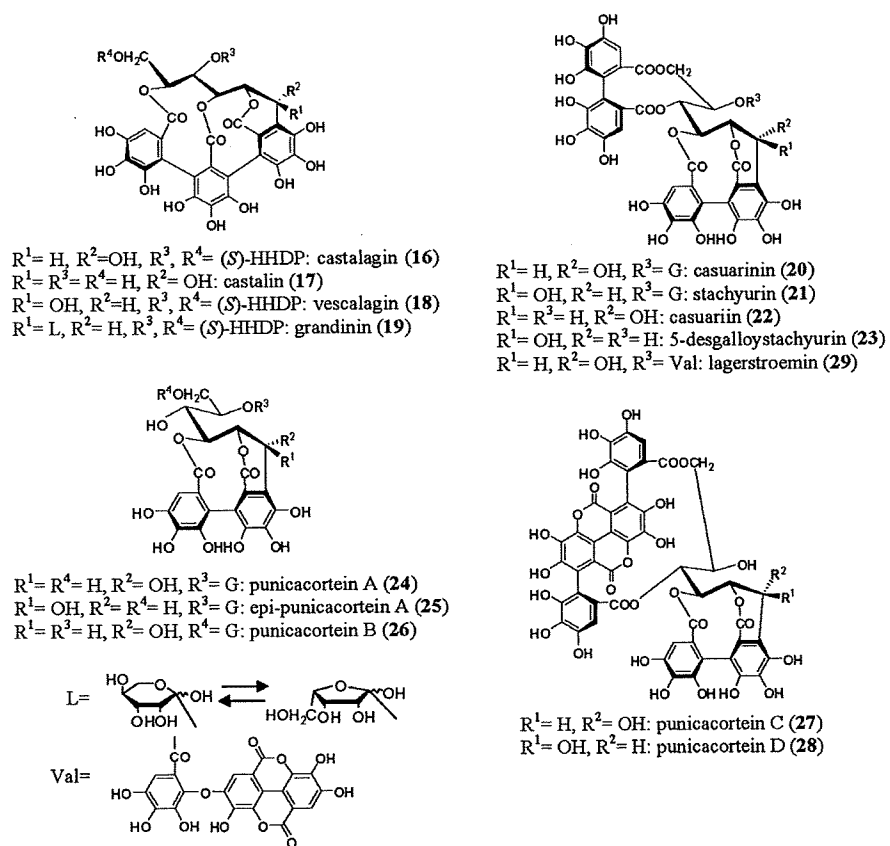
Table 2. C-Glycosidic ellagitannins in the order Myrtales.

Family	Plant species	C-Glycosidic tannins	Ref.
Combretaceae	<i>Anogeissus acuminata</i>	16, 17, 18, 19	[43]
	<i>Anogeissus leiocarpus</i>	16	[44]
	<i>Lumnitzera racemosa</i>	16	[45]
	<i>Terminalia arjuna</i>	16, 20, 22	[31]
	<i>Terminalia macroptera</i>	27	[37]
	<i>Terminalia arborea</i>	28	[30]
	<i>Thiloa glaucocarpa</i>	16, 18, 20, 21	[46]
	Lythraceae	<i>Lagerstroemia flos-reginea</i>	16, 18, 20, 21, 22, 23, 24, 29
<i>Lagerstroemia speciosa</i>		16, 18, 19, 29	[48]
Melastomataceae	<i>Osbeckia chinensis</i>	20, 22, 25	[49]
	<i>Tibouchina semidecandra</i>	16, 18, 20	[13]

Table 2. Cont.

Myrtaceae	<i>Callistemon lanceolatus</i>	20	[14]
	<i>Eucalyptus alba</i>	21, 22	[15]
	<i>Eugenia grandis</i>	16, 18	[50]
	<i>Kunzea ambigua</i>	20	[51]
	<i>Melaleuca squarrosa</i>	20, 21	[52]
	<i>Pimenta dioica</i>	16, 18, 20, 22	[20]
	<i>Siphoneugena densiflora</i>	16, 20	[53]
	<i>Syzygium aqueum</i>	16, 18, 19	[21]
	<i>Syzygium aromaticum</i>	20, 22	[22]
Punicaceae	<i>Punica granatum</i>	20, 22, 25, 26, 27, 28	[40]
Trapaceae	<i>Trapa japonica</i>	20	[9]

Figure 2. Structures of C-glycosidic ellagitannins 16–29.



## 2.3. Complex Tannins

Complex tannins (flavono-ellagitannins) are characterized by a unique C-C condensed structure of C-glycosidic tannins (vescalagin-type or stachyurin-type) with flavan-3-ol (catechin or epicatechin). Unlike the C-glycosidic tannins, these tannins have been found in a rather limited number of plant species belonging to the Combretaceae, Myrtaceae, Melastomataceae, Fagaceae, and Theaceae families [3].

A typical example of a vescalagin-based complex tannin, acutissimin A (30) was first isolated from fagaceous plants and later found in the combretaceous plant, *Anogeissus acuminata* var. *lanceolata* [43], and the myrtaceous plant, *Syzygium aqueum* [21]. Another myrtaceous plant, *Psidium guajava*, reportedly produces a diversity of complex tannins including 30 and its analogs guajavin B (31), psidinins A (32) and B (34), and mongolicains A (33) and B (35); and the stachyurin-based analogs guajavin A (36), guavins A (38), C (39) and D (40), and psidinin C (41) [54] (Figure 3). *Melastoma malabathricum*, a member of the Melastomataceae, also produces metabolites from the stachyurin-based complex tannins malabathrins A (43), E (42), and F (44) [55].

A stachyurin-based congener, stenophyllanin A (37), was isolated from *Melaleuca squarrosa* (Myrtaceae) [52] and *Melastoma malabathricum* (Melastomataceae) [55].

Figure 3. (a) Structures of complex tannins 30–40. (b) Structures of complex tannins 41–44.

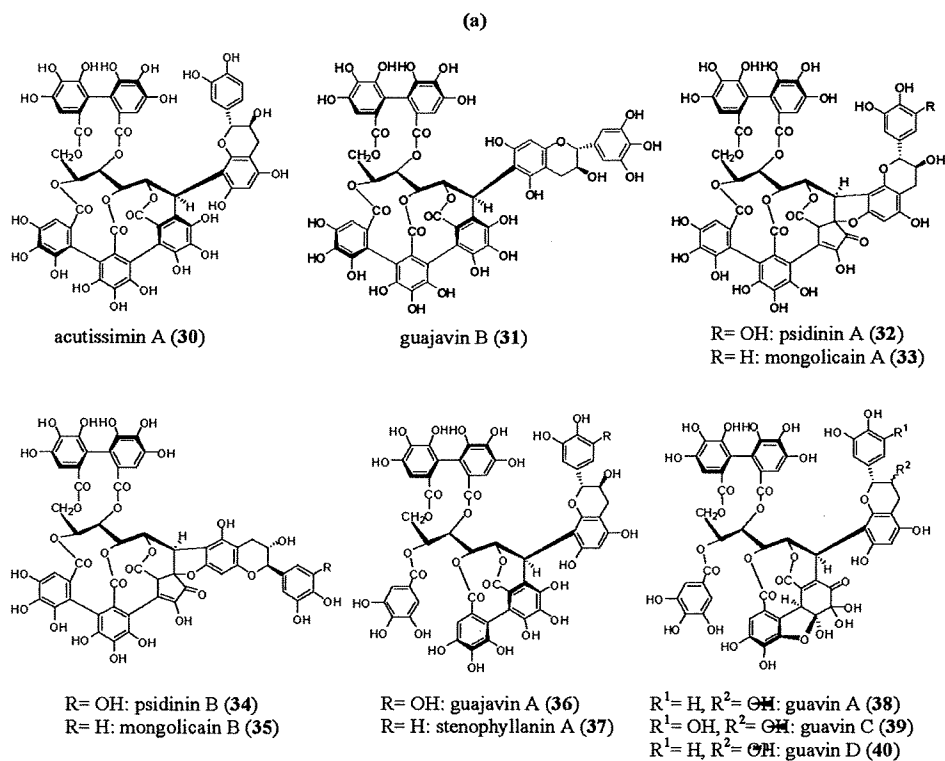
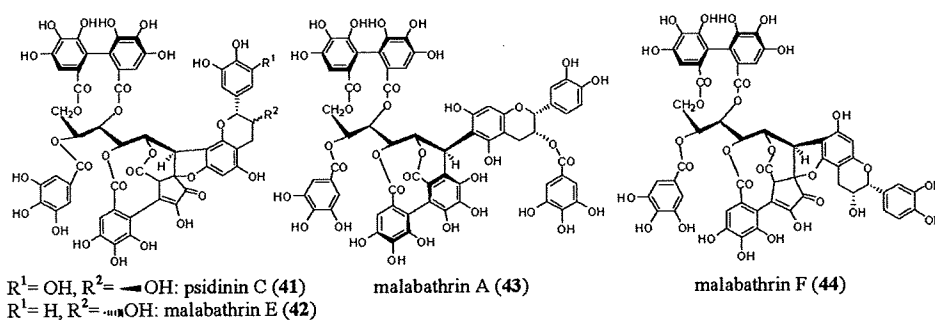




Figure 3. Cont.

(b)



It is noteworthy that both vescalagin- and stachyurin-based complex tannins hitherto isolated are all characterized by possessing a  $\beta$ -oriented C-C bond at glucose C-1 [1]. The formation of this class of tannins is rationalized by non-enzymatic diastereoselective nucleophilic substitution reaction at the exo  $\beta$ -position of the benzylic C-1 cation where is less hindered than the  $\alpha$ -site. In fact, many examples of hemisynthesis of the complex tannin by simple acid-catalyzed reaction between C-glycosidic tannin and (+)-catechin or (–)-epicatechin have been reported.

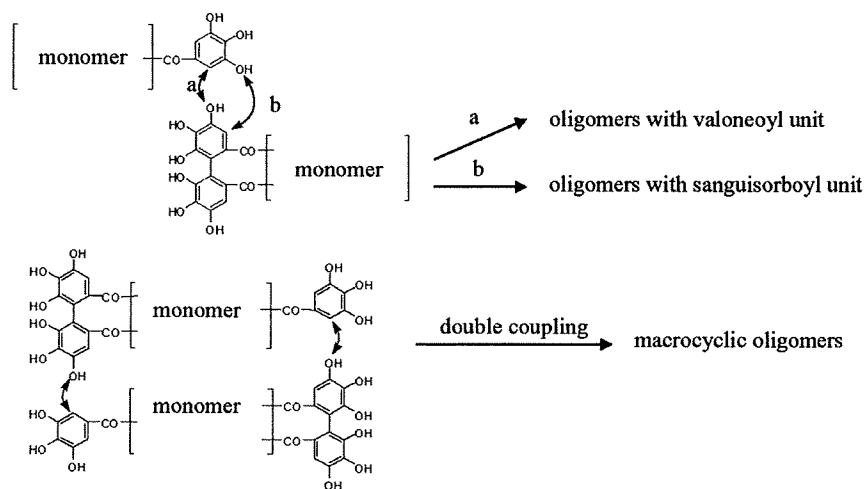
### 3. Oligomeric Ellagitannins

Oligomeric ellagitannins are common among many plant families, including the Fagaceae, Rosaceae, Coriariaceae, Onagraceae, Melastomataceae, Myrtaceae, and Lythraceae [3]. This class of tannins is divided into three sub-groups based on structural features: (1) oligomers that contain a valoneoyl group or its equivalent, formed by intermolecular C-O bonds between an HHDP group and a galloyl group of a neighboring monomer, (2) macrocyclic oligomers formed by two C-O bonds, and (3) C-glycosidic tannin oligomers produced by intermolecular C-C bond formation between C-1 of one monomer and the aromatic ring of another (see Figure 4). These structural features are chemotaxonomically significant and are often characteristic of the plant genus or family. The following section provides an overview of the oligomers isolated thus far from each of the families within the Myrtales.

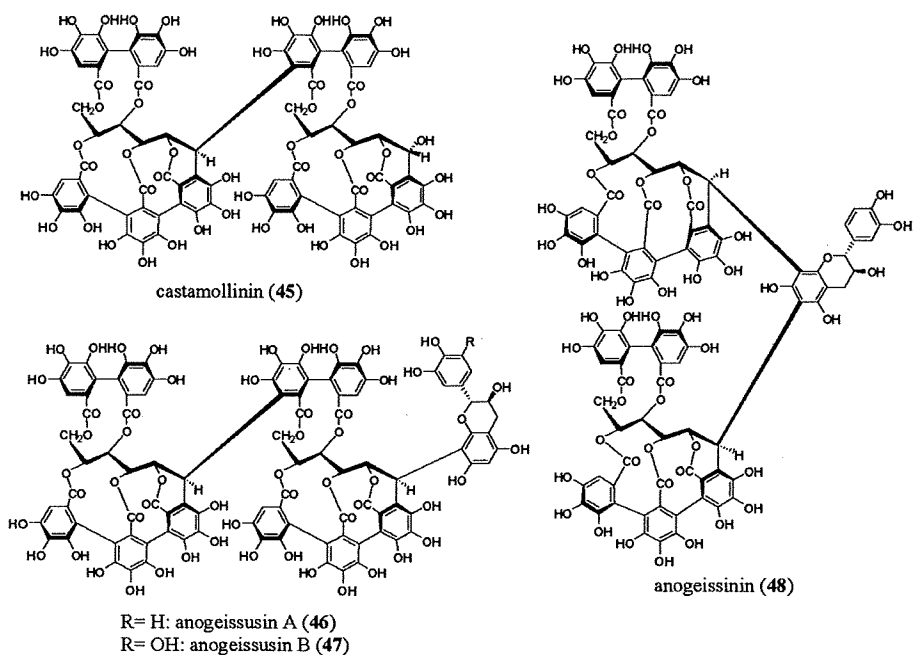
#### 3.1. Oligomers from the Combretaceae

Although more than 10 of the combretaceous plant species described above have yielded various ellagitannin monomers, only *Anogeissus acuminata* was reported to yield C-C linked dimers of C-glycosidic ellagitannin, including castamollinin (45), anogeissusins A (46) and B (47), and anogeissinin (48) [43] (Figure 5). Dimers 46–48 are relatively rare tannins in which two equivalents of vescalagin-type monomer are connected to or through the A-ring of a (+)-catechin or (+)-gallocatechin.

**Figure 4.** General oligomerization mode for the types 1 and 2. (1) examples of coupling mode for formation of valeoyl or its equivalent unit by C-O coupling. (2) macrocyclic dimer (double coupling for HHDP and galloyl).



**Figure 5.** Structures of C-glycosidic ellagitannin dimers 45–48.



**Figure 6.** (a) Structures of ellagitannin oligomers 49–59. (b) Structures of ellagitannin oligomers 60 and 61.

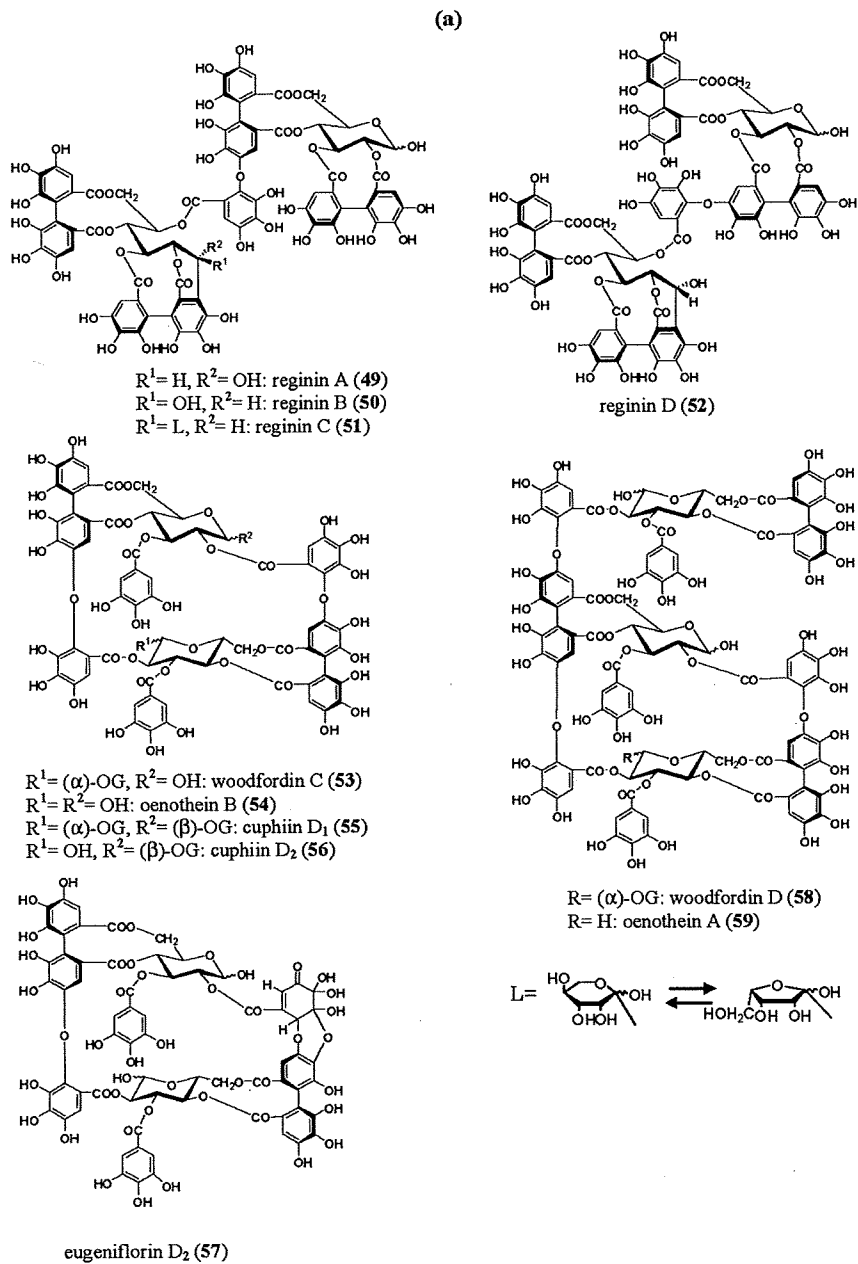
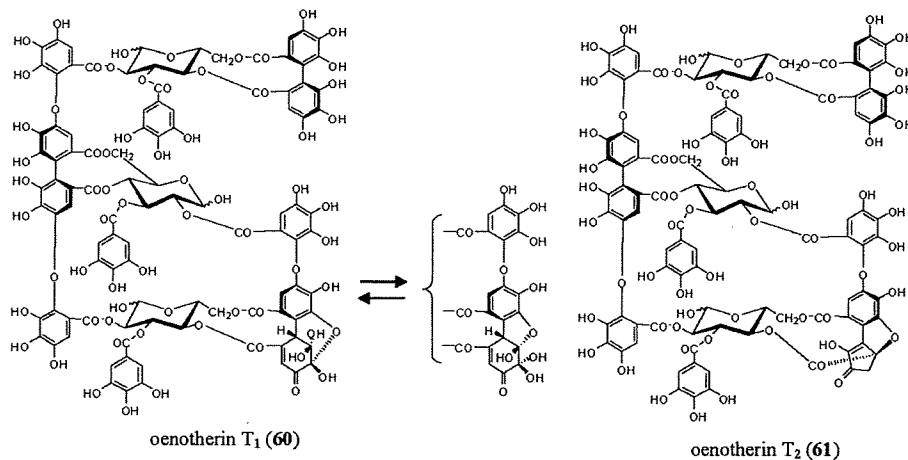


Figure 6. Cont.

(b)



### 3.2. Oligomers from the Lythraceae and Onagraceae

The regio-isomeric dimers, reginins A (49) and D (52) together with reginins B (50) and C (51), which are produced by intermolecular C-O bonds between casuarinin (stachyurin) and pedunculagin, were isolated from *Lagerstroemia flos-reginea* (Lythraceae) [47] (Figure 6). Reginin A (49) has also been isolated from the leaves of *L. speciosa*, which are popular as “banaba” in the Philippines [48]. Unique macrocyclic oligomers, woodfordins C (53) and D (58) and their desgalloyl congeners oenotheins B (54) and A (59), were obtained from the leaves of *Woodfordia fruticosa*, one of the Jamu medicines in Indonesia [56]. Analogous macrocyclic dimers, cuphiins D<sub>1</sub> (55) and D<sub>2</sub> (56) co-occur with 53 and 54 in *Cuphea hyssopifolia*, a lythraceous shrub native to Mexico [57]. Oenotheins A (59) and B (54) were first isolated as the main tannins in *Oenothera erythrosepala* leaves [24] and are widely distributed in the *Oenothera* and *Epilobium* species of Onagraceae, i.e., *O. laciniata* [25], *O. biennis* [58], *O. tetraptera* [26], *E. angustifolium* [23], and many other *Epilobium* species [59]. The occurrence of oxidized metabolites oenotherins T<sub>1</sub> (60) and T<sub>2</sub> (61) of 59 in *O. tetraptera* leaves was recently reported by Taniguchi *et al.* [26,60]. The chemical conversion of 60 to 59 was achieved by reduction with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>.

### 3.3. Oligomers from Myrtaceae

In addition to the Lythraceae and Onagraceae, oenothein B (54) has been isolated from the myrtaceous plants *Eucalyptus alba* [15], *Eucalyptus cypellocarpa* [61], *Eucalyptus consideriana* [16], *Eugenia uniflora* [62], *Melaleuca leucadendron* [63], and *Myrtus communis* [19]. Of these plants, *E. uniflora*, *E. cypellocarpa*, and *M. communis* also produce eugeniflorin D<sub>2</sub> (57) with a dehydrovaloneoyl group isomeric to that in oenotherin T<sub>1</sub> (60). It recently has been shown that the



Figure 8. Coupling modes (a–d) to melasquanins A (62)–D (65).

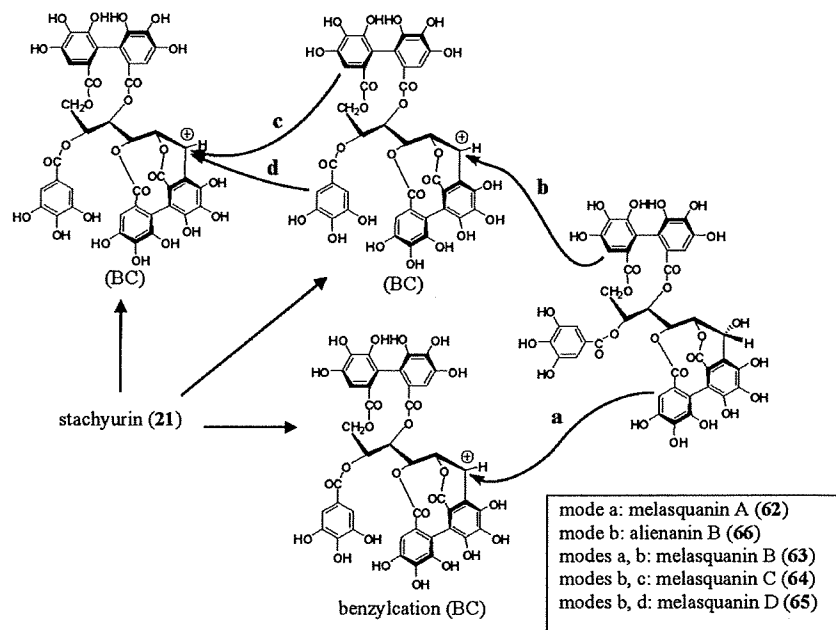
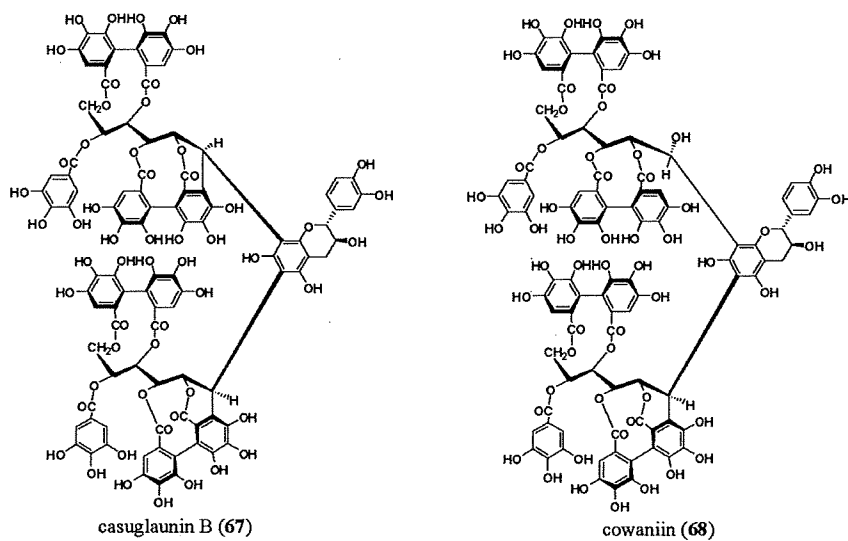


Figure 9. Structures of ellagitannin oligomers 67 and 68.

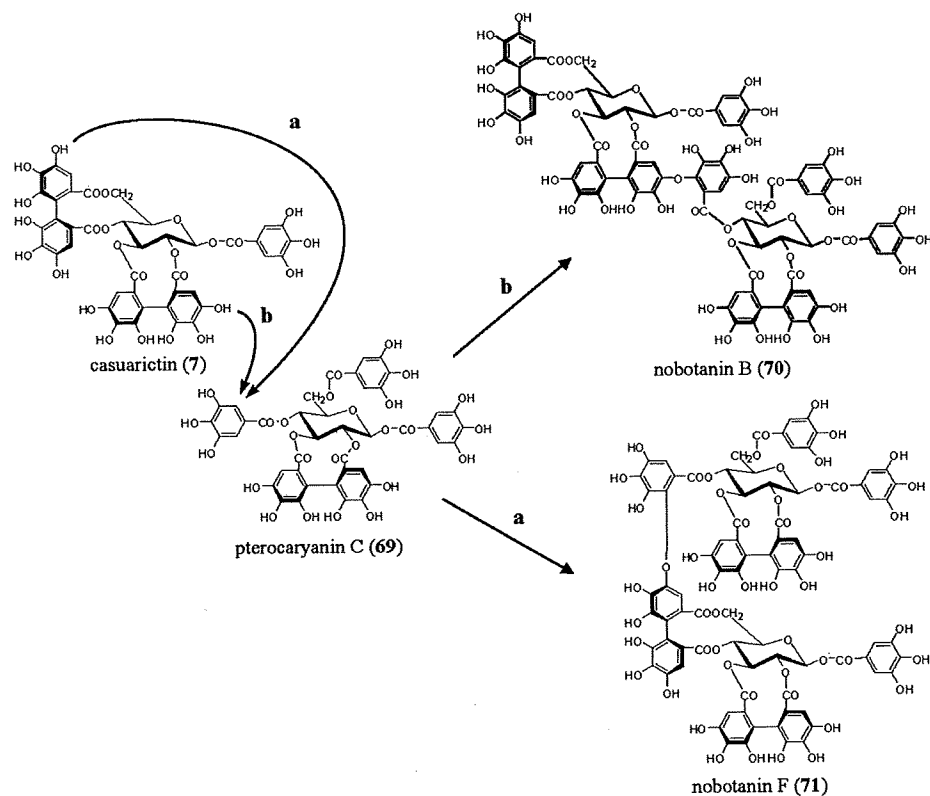


The plant also yields a unique complex tannin dimer, cowaniin (**68**), first obtained from *Cowania mexicana* (Rosaceae) [64]. The chemical structure **68** inferred from spectral data was confirmed by conversion into **67** following an acid treatment.

### 3.4. Oligomers from Melastomataceae

A series of studies on plant species in six genera (*Medinilla*, *Heterocentron*, *Tibouchina*, *Melastoma*, *Bredia*, and *Monochaetum*) of the Melastomataceae has revealed more than 20 characteristic ellagitannin oligomers up to pentamers, e.g., nobotanins A–C and E–T. These oligomers share two common features: (1) they are essentially composed of two different monomers, casuarictin (**7**; C) and pterocaryanin C (**69**; PC), which are coupled alternatively to form the valoneoyl unit; and (2) the galloyl group of **69** can only participate in the formation of the valoneoyl group at O-5, whereas the HHDP groups of both monomers are susceptible to bond formation regardless of their positions [65] (Figure 10).

Figure 10. Coupling mode of nobotanins.



These characteristics are chemotaxonomically significant relative to oligomers connected through the valoneoyl group, which are mostly constructed from a single monomeric component. The representative oligomers are nobotanins B (70; C-PC) [12], F (71; PC-C), and K (72; PC-C-PC-C), although 70 is the most abundant dimer in most species of this family. Nobotanin B (70) also seems to be a key compound from which trimers and tetramers are producible by further bonding with 7 and 69, as observed in nobotanins E (73; PC-C-PC) and K (72) [66] (Figure 10). The largest pentameric oligomers, melastoflorins A (74) through D (77), were isolated together with several dimers and tetramers from the Colombian shrub *Monochaetum multiflorum* [65] (Figure 11).

**Figure 11.** (a) Structures of ellagitannin oligomers 72 and 73. (b) Structures of ellagitannin oligomers 74–77.

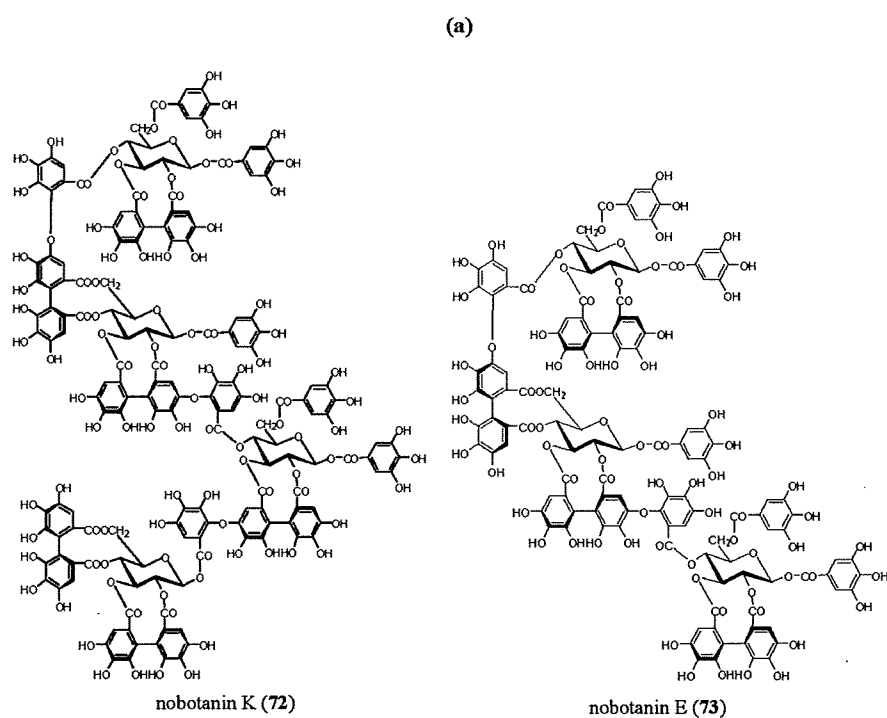
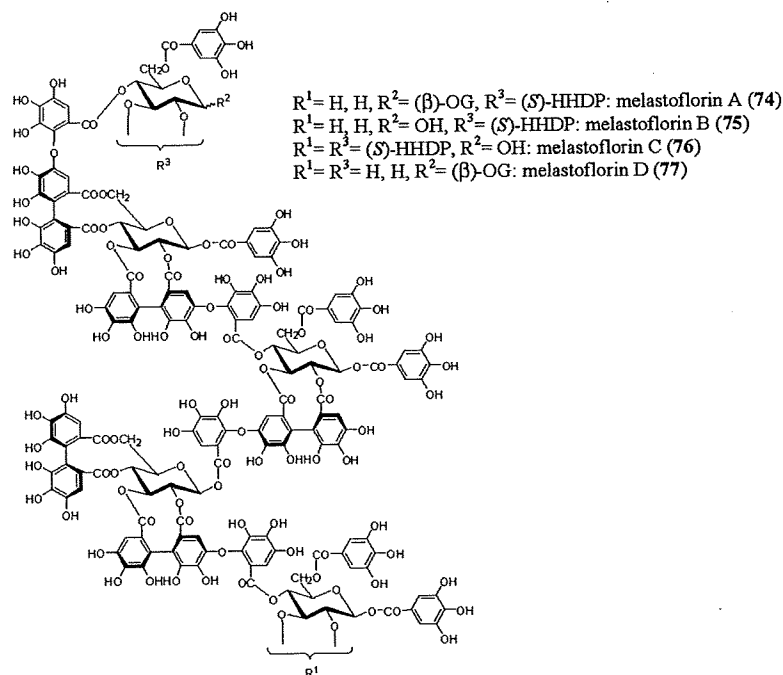




Figure 11. Cont.

(b)



#### 4. Structure Determination of the Oligomeric Ellagitannins

Structure elucidation of the oligomers has generally been achieved by (1) identification of their constituent units by methylation of the tannin followed by methanolysis or direct acid hydrolysis, (2) detailed spectroscopic analyses using MS, UV and NMR spectra including 2-dimensional  $^1\text{H}\text{-}^1\text{H}$  (or  $^1\text{H}\text{-}^{13}\text{C}$ ) COSY and  $^1\text{H}$ -detected multi-bond heteronuclear multiple quantum coherence (HMBC), and (3) chemical confirmation of the structure presumed on the basis of the findings from the above (1) and (2) by the characterization of partial hydrolysates of smaller molecule in hot water as exemplified for nobotanin B (70) in Figure 12. Molecular weights up to 4,000 are nowadays determined with the aid of electrospray mass measurement in the presence of ammonium acetate, or FABMS ( $[\text{M} + \text{H}]^+$  or  $[\text{M} + \text{Na}]^+$ ). In the NMR analyses, HMBC provides a convenient and reliable way to determine the position of each acyl group on the glucose core by three-bond correlations between the aromatic proton and glucose proton through a common ester carbonyl carbon as illustrated for melasquanin A (62) in Figure 13. The atropisomerism of the chiral biphenyl moiety in the molecule is directly determined without any degradation reaction by circular dichroism (CD) spectrum in which positive or negative Cotton effect at around 230 nm is diagnostic for (*S*)- or (*R*)-configuration, respectively [8].

Figure 12. Chemical degradation of nobotanin B (70).

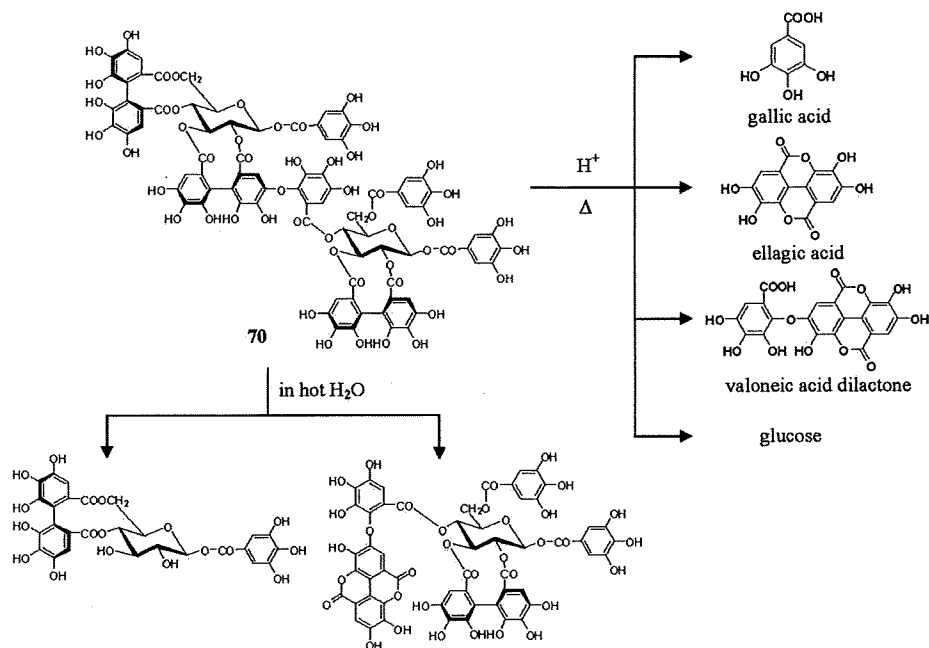
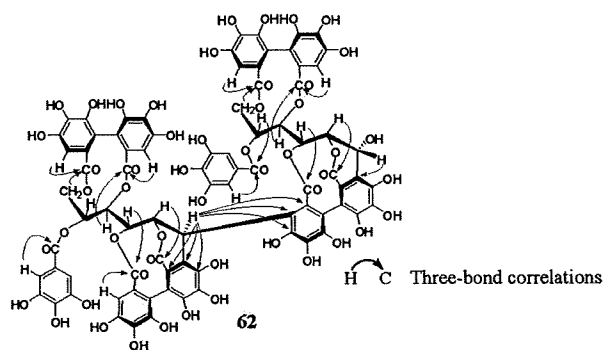


Figure 13. HMBC data for melasquanin A (62).



### 5. Biological Activities of Ellagitannins Found in the Myrtales

Remarkable progress in the structural characterization of the numerous tannins in foods, beverages, and medicinal plants since the 1980s has enabled *in vitro* and *in vivo* studies of their biological properties based on structural differences. A wide range of significant biological activities beneficial to human health have been reported for both ellagitannins and proanthocyanidins. The strong affinity of

tannins to various biopolymers such as enzymes, and antioxidative effects based on radical scavenging, are key to their diverse biological effects [1]. A survey of the biological activity of the Myrtales tannins using the electronic search engines SciFinder Scholar and Science Direct revealed various antimicrobial, antitumor, enzyme-inhibitory, and immunomodulatory effects of ellagitannins encountered in species of Combretaceae, Lythraceae, Myrtaceae and Onagraceae, as shown in Table 3.

**Table 3.** Biological activities of ellagitannins found in the Myrtales.

Biological activity	Compound (source)	Ref.
Anti-Herpes simplex virus type 2 activity	casuarinin (20) ( <i>Terminalia arjuna</i> )	[67]
Apoptosis in human breast adenocarcinoma MCF-7 cells	casuarinin (20)	[68]
Antileishmanial activity	casuarinin (20), castalagin (16)	[69]
	castalagin (16) ( <i>Anogeissus leiocarpus</i> )	[44]
Antihypertensive activity (rats)	castalagin (16) ( <i>Lumnitzera racemosa</i> )	[45]
	corilagin, chebulinic acid (15)	
$\alpha$ -Glucosidase inhibitor	casuarietin (7) ( <i>Syzygium aromaticum</i> )	[70]
	chebulagic acid (14) ( <i>Terminalia chebula</i> )	[71]
Dual inhibitor against COX and 5-LOX	chebulagic acid (14) ( <i>T. chebula</i> )	[72]
Anti-inflammation in LPS-induced RAW 264.7 cells	chebulagic acid (14) ( <i>T. chebula</i> )	[73]
Effect on carageenan-induced inflammation	punicalagin (9), punicalin (10) ( <i>T. catappa</i> )	[74]
Antioxidant and hepatoprotective effects on acetaminophen-induced liver damage in rats	punicalagin (9), punicalin (10) ( <i>T. catappa</i> )	[75]
Effect against bleomycin-induced genotoxicity in Chinese hamster ovary cells	punicalagin (9) ( <i>T. catappa</i> )	[76]
Chemopreventive effect on H-ras-transformed NIH3T3 cells	punicalagin (9) ( <i>T. catappa</i> )	[77]
Inhibitory effect on HIV-1 reverse transcriptase	punicalin (10), 2-O-galloylpunicalin ( <i>T. triflora</i> )	[39]
Inhibitory effect on CCl <sub>4</sub> -induced hepatotoxicity	punicalagin (9) ( <i>T. myriocarpa</i> )	[38]
Activators of glucose transport in fat cells	lagerstroemin (29), reginin A (49) ( <i>L. speciosa</i> )	[78]
Activation of insulin receptors	lagerstroemin (29)	[79]
Insulin-like glucose uptake-stimulatory/inhibitory and adiposities differentiation inhibitory activity in 3T3-L1 cells	lagerstroemin (29)	[80]
Host-mediated antitumor effect	casuarinin (20), casuariin (22), stachyurin (21)	
Host-mediated antitumor	oenothein B (54) ( <i>Oenothera erythrosepala</i> )	[24]
	oenothein B (54) ( <i>Woodfordia fruticosa</i> )	[56]
	woodfordins A-C (53)	
Inhibitor of deoxyribonucleic acid topoisomerase II	woodfruticodin [= woodfordin C (53)]	[81]
EBV DNA polymerase inhibitory effect	oenothein B (54) ( <i>Eugenia uniflora</i> )	[82]
	eugeniflorins D <sub>1</sub> , D <sub>2</sub> (57)	
5 $\alpha$ -reductase, aromatase inhibitory effect	oenotheins A (59), B (54) ( <i>Epilobium</i> sp)	[59]
Induction of neutral endopeptidase activity in PC-3 cells	oenothein B (54) ( <i>Epilobium angustifolium</i> )	[83]
<i>In vitro</i> immunomodulatory effect on human mononuclear cells	cuphiin D <sub>1</sub> (55) ( <i>Cuphea</i> sp)	[84]
Induce apoptosis in HL-60 cells	cuphiin D <sub>1</sub> (55)	[85]
Poly (ADP-ribose) glycohydrolase inhibition	nobotarins B (70), K (72) ( <i>Tibouchina</i> sp)	[86]

*L. speciosa*, *Lagerstroemia speciosa*.

### 5.1. Casuarinin (20), Castalagin (21), and Related Tannins

Kolodziej *et al.* [69] evaluated the *in vitro* antileishmanial activity of various types of tannins using *Leishmania donovani*. Although none of the tannins showed significant antiparasitic effects against the extracellular promastigote of *L. donovani* ( $EC_{50} > 25 \mu\text{g/mL}$ ), all of the hydrolysable tannins, including oligomers, exhibited potent activity ( $EC_{50} < 0.4\text{--}12.5 \mu\text{g/mL}$ ) against the intracellular amastigote form which resides within murine macrophage-like RAW 264.7 cells infected with *L. donovani*. Observed potencies were stronger or comparable to that of the reference compound, Pentosam® ( $EC_{50} 7.9 \mu\text{g/mL}$ ), which is therapeutically used as antileishmanial drug. Among the hydrolysable tannins, the most potent antileishmanial activity was exhibited by geraniin and related tannins ( $EC_{50} < 0.4 \mu\text{g/mL}$ ). The C-glycosidic tannins casuarinin (20) and castalagin (16) also showed pronounced antileishmanial activities with  $EC_{50}$  values of 0.5 and 2.7  $\mu\text{g/mL}$ , respectively. Note that most of these tannins, with the exception of oligomers, exhibited low cytotoxicity against murine host cells ( $EC_{50} > 25 \mu\text{g/mL}$ ). Separate functional assays have shown that the amastigote-specific activity of these tannins is likely associated with immunomodulatory effects, such as macrophage activation to release cytokines, tumor necrosis factor (TNF)- $\alpha$ , and interferon (IFN)- $\gamma$ . The degree of these immunomodulatory effects was highly correlated with the degree of intracellular *Leishmania* death. The search for antiparasitic substances in butanol extracts of *Anogeissus leiocarpus* and *Terminalia avicennoides*, which are used to treat some parasitic diseases in Africa, resulted in the characterization of castalagin (16) as a primary antileishmanial component with an  $EC_{50}$  ranging from 55 to greater than 150  $\mu\text{g/mL}$  against the promastigote forms of four *Leishmania* strains [44].

Casuarinin (20) isolated from *Terminalia arjuna* also exhibits *in vitro* antiviral effects against Herpes simplex virus type 2 (HSV-2) with an  $IC_{50}$  of 3.6 and 1.5  $\mu\text{M}$  in XTT and plaque reduction assays, respectively. These effects were associated with the inhibition of viral attachment and cell penetration [67]. Lin *et al.* [68] also found that 20 induced apoptosis in human breast adenocarcinoma MCF-7 cells and in human non-small cell lung cancer cells A549 by blocking cell cycle progression in the G0/G1 phase.

In the screening of spontaneously hypertensive rats, castalagin (16), chebulinic acid (15), and corilagin were identified as the major antihypertensive substances among the hydrolysable tannins isolated from the leaves of *Lumnitzera racemosa* (Combretaceae) [45].

Chebulagic acid (14) from *Terminalia chebula* has been shown to reversibly and non-competitively inhibit  $\alpha$ -glucosidase (maltase) activity, suggesting a potential for managing type-2 diabetes [71]. Other tannins that have been identified as  $\alpha$ -glucosidase inhibitors are tellimagrandin I (1) and eugeniin (casuarictin) (7) from *Syzygium aromaticum* (Myrtaceae) [70]. Recently, Reddy *et al.* reported that 14 also exhibited potent anti-inflammatory effects in mouse macrophage cell line RAW 264.7 that had been stimulated with LPS by inhibition of NF- $\kappa$ B activation and MAP kinase phosphorylation [73], and in COLO-205 cells by enzyme inhibition of COX and 5-LOX [72].

### 5.2. Punicalagin (9) and Related Tannins

Hepatoprotective effects of various tannins based on their ability to scavenge radical reactive oxygen species (ROS) have been demonstrated both *in vitro* and *in vivo*. For example, punicalagin (9)