

# OLIGOMERIC HYDROLYZABLE TANNINS, A NEW CLASS OF PLANT POLYPHENOLS<sup>†</sup>

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Abstract—Oligomeric hydrolyzable tannins belong to a newly developed field of tannin research. The isolation and structure determination of the first oligomer, agrimoniin, were presented in 1982, and since then more than sixty oligomers have been obtained from various plants by 1989. This review deals with these oligomers which were classified according to the biogenetical coupling modes between monomeric hydrolyzable tannins, and their botanical sources. Recent techniques for their isolation and structure elucidation, and the biological activities of the oligomers are also discussed.

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<sup>†</sup> Dedicated to the late Professor Tetsuji Kametani.

## I. Introduction

The isolation and structure determination of many tannins from various plants recently produced great advances in the study of chemistry and biological activities of tannins.<sup>1</sup> One of the most remarkable developments was that of oligomeric hydrolyzable tannins.

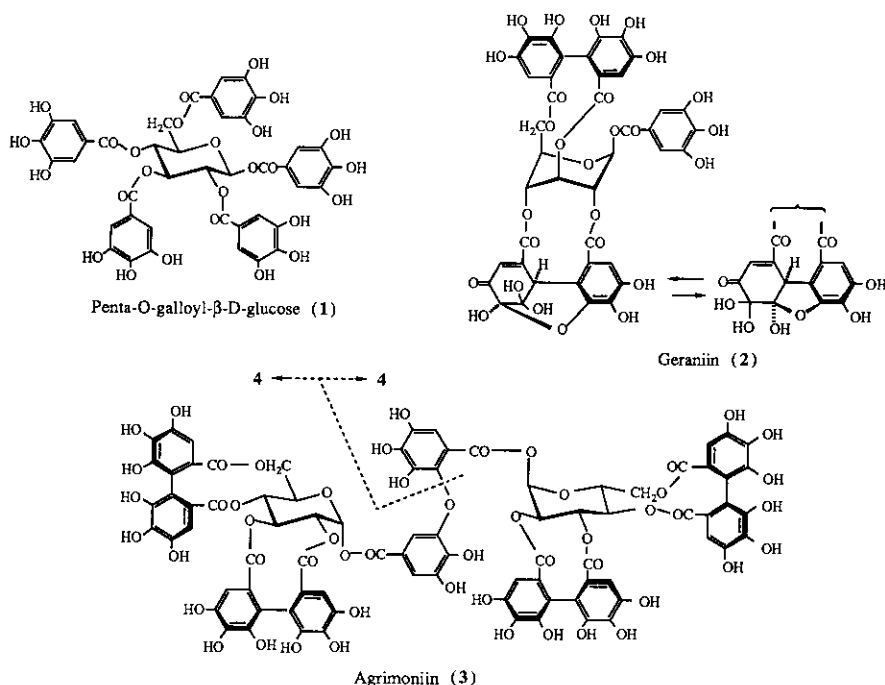
Tannins are mostly classified into two large groups, hydrolyzable tannins and condensed tannins. Although diverse molecular weights and structures have been found for both of these types of tannins, the hydrolyzable tannins known in the early stage of tannin research were solely monomeric hydrolyzable tannins.<sup>2</sup> Each molecule of this class of tannins has a monosaccharide or a cyclitol as the structural core, to which several polyphenolcarboxylic acids, such as gallic acid, hexahydroxydiphenic acid and /or their analogs, are bound with ester linkages.

The tannins having only galloyl group as the acyl group are called gallotannins, and those having hexahydroxydiphenoyl (HHDP) group are called ellagitannins. So-called "tannic acid", which is commercially available and is one of the most widely used tannin materials, is usually a mixture of a number of gallotannins. Penta-O-galloyl- $\beta$ -D-glucopyranose (1) represents the fundamental structures of gallotannins comprising a "tannic acid" mixture,<sup>3</sup> but the composition of the mixture in each preparation of "tannic acid" is hardly reproducible. "Tannic acid" is prepared from several different sources, such as Chinese gall and Turkish gall. Notable lability of the depside linkages among galloyl groups in each gallotannin component of the "tannic acid", induces marked diversity of the structures by altering the composition of the "tannic acid" during its preparation from plant sources.

Geraniin (2),<sup>4</sup> a crystalline tannin, is an ellagitannin, although it also has a structural feature of dehydroellagitannin<sup>1,5</sup> because of the presence of a dehydrohexahydroxydiphenoyl (DHHDP) group in its molecule. There are also several types of monomeric hydrolyzable tannins, such as C-glycosidic hydrolyzable tannins<sup>1,6</sup> and caffeetannins,<sup>1,7</sup> and complex tannins composed of the structural units of both hydrolyzable tannins and condensed tannins.<sup>8</sup>

Structures of oligomeric hydrolyzable tannins consist of two or more the molecules of monomeric hydrolyzable tannins of various types. The first oligomer isolated from nature was agrimoniin (3),<sup>9,10</sup> a dimer from Agrimonia pilosa. It is composed of two molecules of potentillin (4), a monomeric ellagitannin, and has a dehydrodigalloyl (DHDG) group which can be produced by the coupling between two

galloyl groups, each  $\alpha$ -bonded to O-1 of a glucopyranose in the two monomeric units. Agrimoniin (3) was the first tannin that exhibited host-mediated anti-tumor activity.<sup>11,12</sup>



Scheme 1

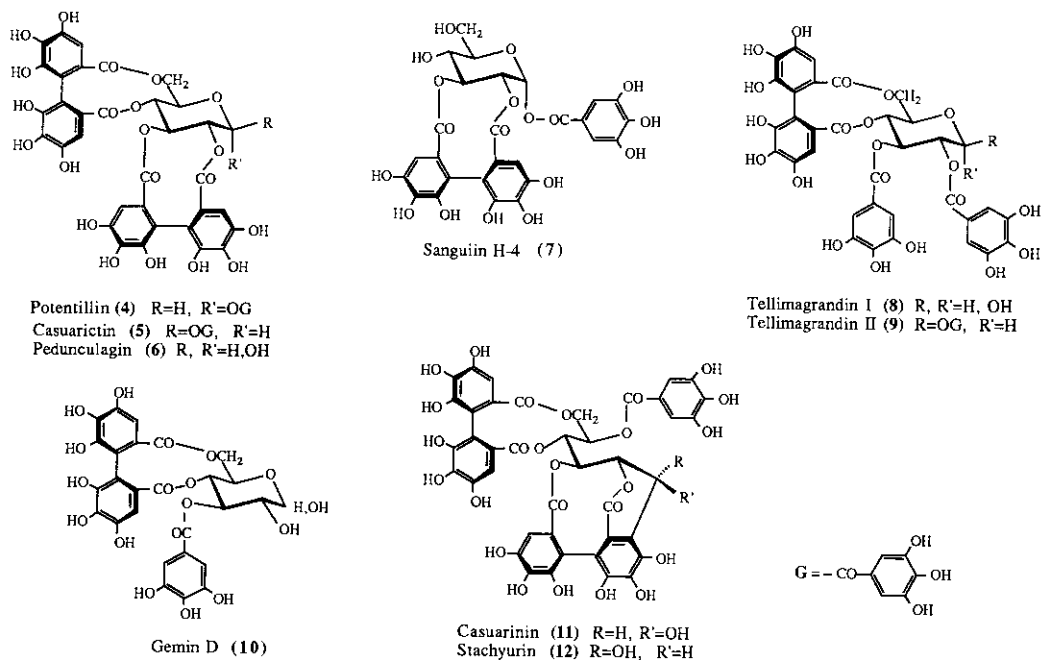
More than sixty oligomeric hydrolyzable tannins, including trimers and tetramers, were isolated by 1989. Some noticeable biological activities have also been found.<sup>13</sup> The aim of this review is to compile and classify their structures, and to point out some characteristic properties of these oligomeric hydrolyzable tannins isolated from various plants during the period 1982-1989.

## II. Classification of Oligomeric Hydrolyzable Tannins

### 1) Classification based on structures of monomers that construct oligomeric hydrolyzable tannins

Most oligomeric hydrolyzable tannins are oligomeric ellagitannins, condensates of monomeric ellagitannins. However, there are also oligomers that have monomeric dehydroellagitannin and C-glycosidic tannin as constituent units in their molecules (oligomeric dehydroellagitannins and C-glucosidic oligomers).

Structures of several monomers most frequently constructing the molecules of oligomeric hydrolyzable tannins are shown in Scheme 2.



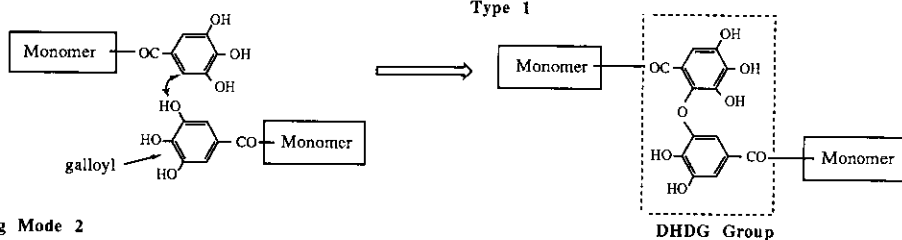
Scheme 2

## 2) Classification by condensation mode between monomers

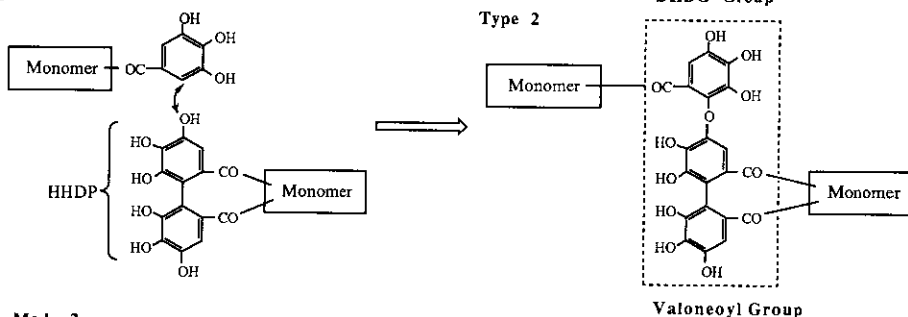
Biogenetically dimeric hydrolyzable tannins are regarded as the products of oxidative coupling between a phenolic hydroxyl group in a monomer and an aromatic ring carbon in another monomer.<sup>9,14</sup> Large oligomers are regarded as the products of repetition of oxidative coupling. Sometimes macro-ring structures are formed by such bonding within a molecule.<sup>15,16</sup>

The oligomers hitherto isolated can be classified into five types according to the structure of the parts linking two monomers. They are regarded as the products of the most plausible biogenetical coupling modes illustrated in Scheme 3.

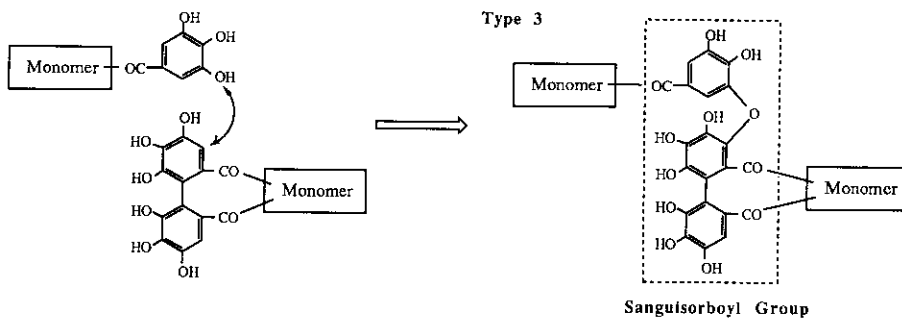
## Coupling Mode 1



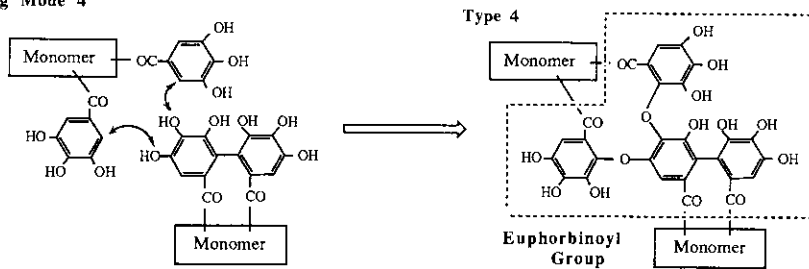
## Coupling Mode 2



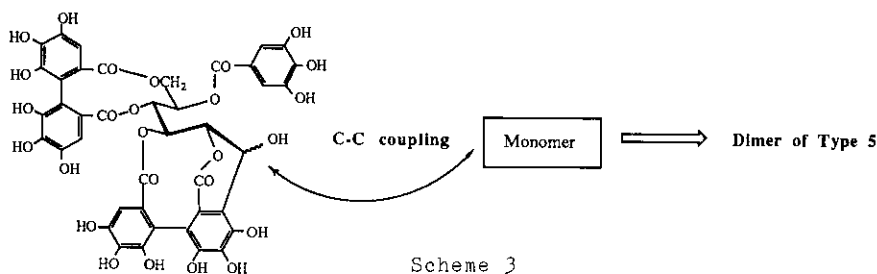
## Coupling Mode 3



## Coupling Mode 4

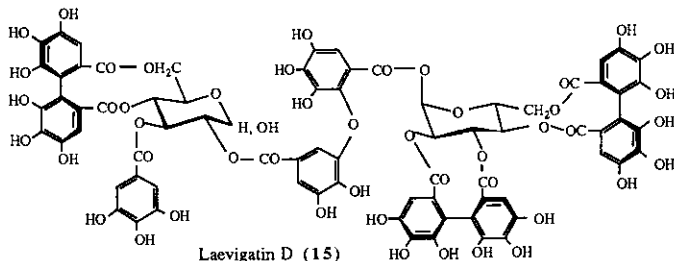


## Coupling Mode 5



Structures of fifty-seven dimers, classified according to the coupling modes 1-5, are as follows:

This type of dimer includes agrimoniin (3)<sup>9</sup> and its analogues, laevigatins (13)-(18)<sup>17,18</sup> that lack one or two HHDP groups of the agrimoniin structure. Although the configurations at the anomeric centers in these dimers and davuriciin D1 (19)<sup>19</sup> are both  $\alpha$ , those in gemins A (20), B (21) and C (22)<sup>20</sup> are  $\alpha$  and  $\beta$ , and those in coriariins A (23) and C (24)<sup>21</sup> are both  $\beta$ . In most dimers of this type, two carboxyl groups of the DHDG group are esterified by the anomeric hydroxyl groups of the two glucose cores, except for laevigatin D (15),<sup>17</sup> in which two ester linkages on the DHDG group are at O-1 of one monomer and O-2 of another monomer.



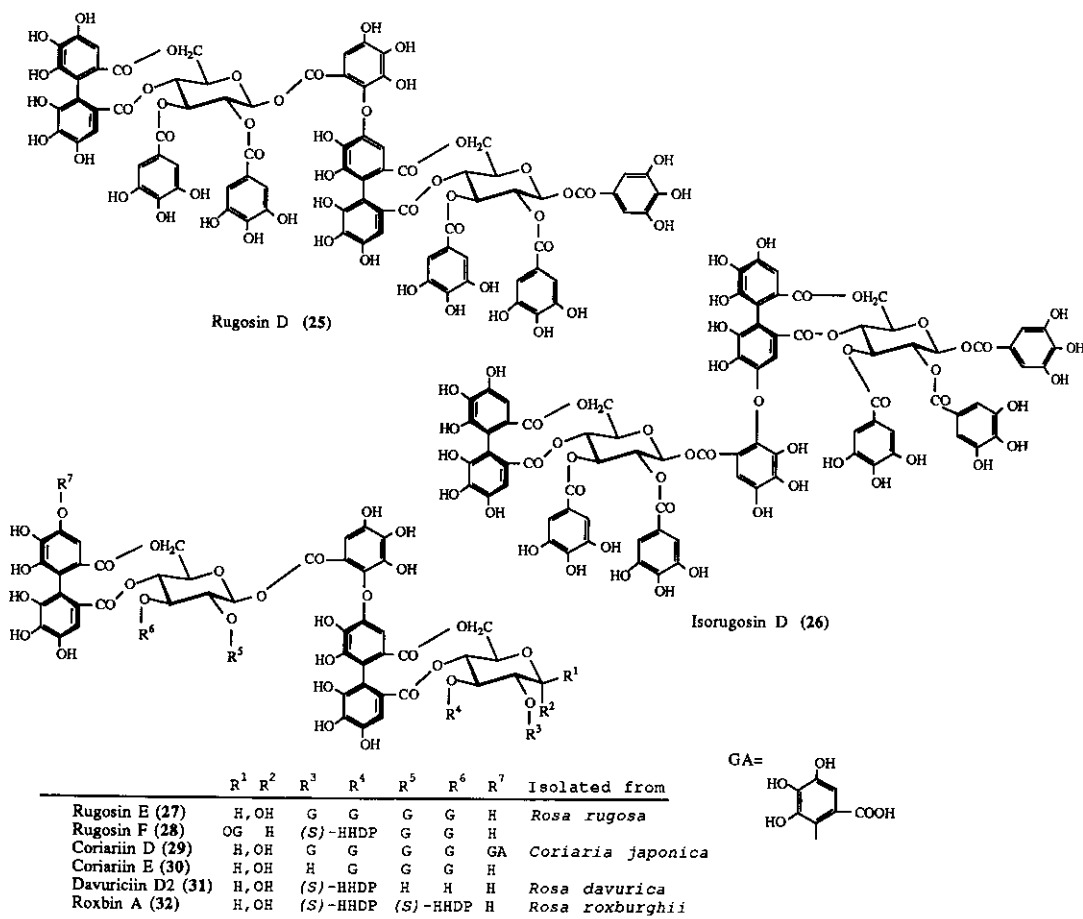
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**Type 2: Dimers with Valoneoyl Group (Products of Coupling Mode 2)**

These dimers are further classified into five sub-types, based on the location of the valoneoyl group linking two monomers, as follows:

- a) Sub-type 1 (Dimers having a valoneoyl group formed by the C-O oxidative coupling between a galloyl group at O-1 of one monomer and an HHDP group at O-4~O-6 of another monomer)

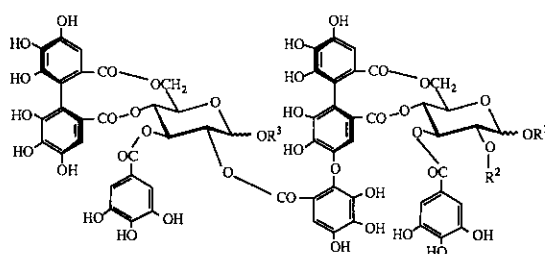
Orientation of the valoneoyl group in rugosin D (25)<sup>22,23</sup> was determined by nmr spectral analyses, including the <sup>1</sup>H-<sup>13</sup>C long-range 2D nmr spectrum of the related monomeric tannin, and also by spectral comparison with isorugosin D (26),<sup>23</sup> an isomer that depends on the orientation of the valoneoyl group. The valoneoyl group in the other six dimers was assigned as in the formulas (27)-(32),<sup>21,22,24-26</sup> based on the comparison of the chemical shifts of aromatic protons with those of the valoneoyl group of (25) and (26), and the chemical conversion and/or degradation.



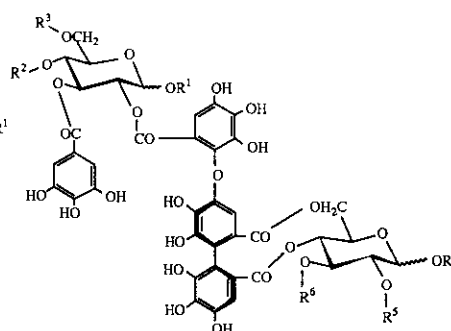
Scheme 5

b) Sub-type 2 (Dimers having a valoneoyl group formed by the C-O oxidative coupling between a galloyl group at O-2 in one monomer and an HHDP group at O-4~O-6 of another monomer)

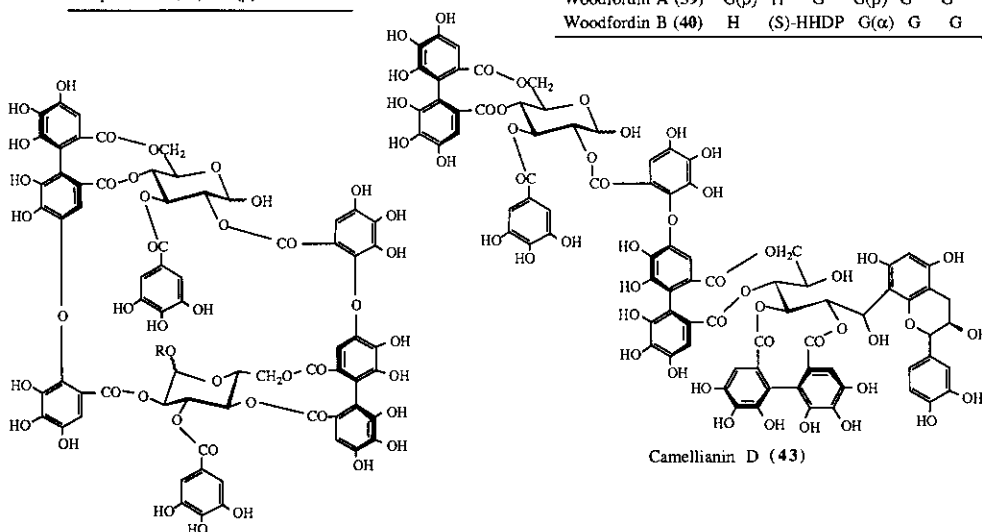
Most of the dimers of this group have one or two free anomeric hydroxyl group(s) and therefore exist as equilibrium mixtures of two or four anomers. Among them, cornusiins A (33)<sup>27</sup> and D (34),<sup>28</sup> and camptothins A (36) and B (37),<sup>29</sup> which were at first isolated from *Cornus officinalis* and *Camptotheca acuminata*, respectively, possess the valoneoyl group oriented in the mode of isorugosins B and D (isorugosin-type), while camelliin A (38) isolated from the flower buds of *Camellia japonica*,<sup>30</sup> has the valoneoyl group oriented in the mode of rugosins A D (rugosin-type).



|                   | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> |
|-------------------|----------------|----------------|----------------|
| Cornusin A (33)   | H              | G              | H              |
| Cornusin D (34)   | H              | G              | G(β)           |
| Cornusin E (35)   | G(β)           | G              | G(β)           |
| Camptothin A (36) | H              | H              | H              |
| Camptothin B (37) | G(β)           | G              | H              |



|                   | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | R <sup>4</sup> | R <sup>5</sup> | R <sup>6</sup> |
|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Camelliin A (38)  | H              | (S)-HHDP       | H              | (S)-HHDP       |                |                |
| Woodfordin A (39) | G(β)           | H              | G              | G(β)           | G              | G              |
| Woodfordin B (40) | H              | (S)-HHDP       | G(α)           | G              | G              |                |



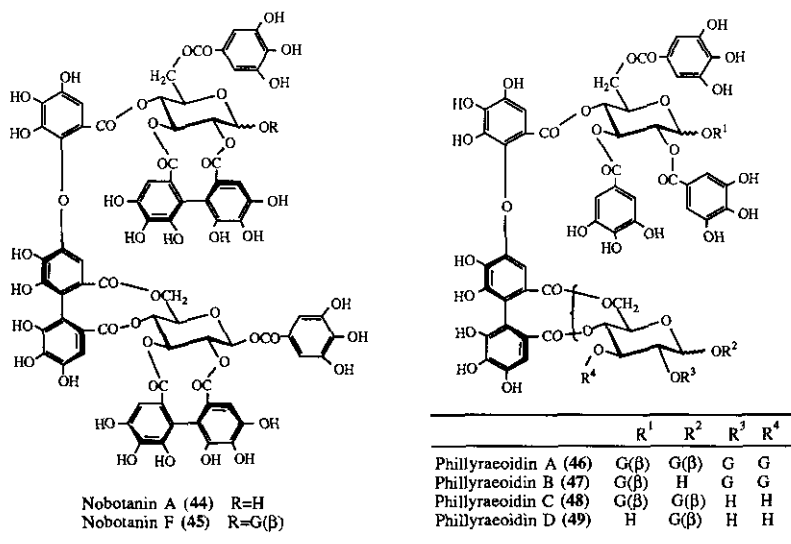
Oenothin B (41) R=H  
Woodfordin C (42) R=G(α)

Scheme 6

Woodfordins A (39) and B (40),<sup>16</sup> which were obtained from Woodfordia fruticosa, also have the rugosin-type valoneoyl group. It is noticeable that novel macrocyclic dimers, oenothrin B (41)<sup>15</sup> and woodfordin C (42),<sup>16</sup> have valoneoyl groups of both orientations in a molecule. The former isolated from Oenothera erythrosepala, exhibited marked host-mediated anti-tumor activity<sup>11</sup> and anti-HIV activity.<sup>31</sup> Camellianin D (43), which was isolated from the leaves of Camellia japonica, was the first dimer possessing a structural unit of condensed tannins [(-)-epicatechin] in its molecule.<sup>32</sup>

c) Sub-type 3 (Dimers having a valoneoyl group formed by the C-O oxidative coupling between galloyl group at O-4 in one monomer and an HHDP group at O-4~O-6 of another monomer).

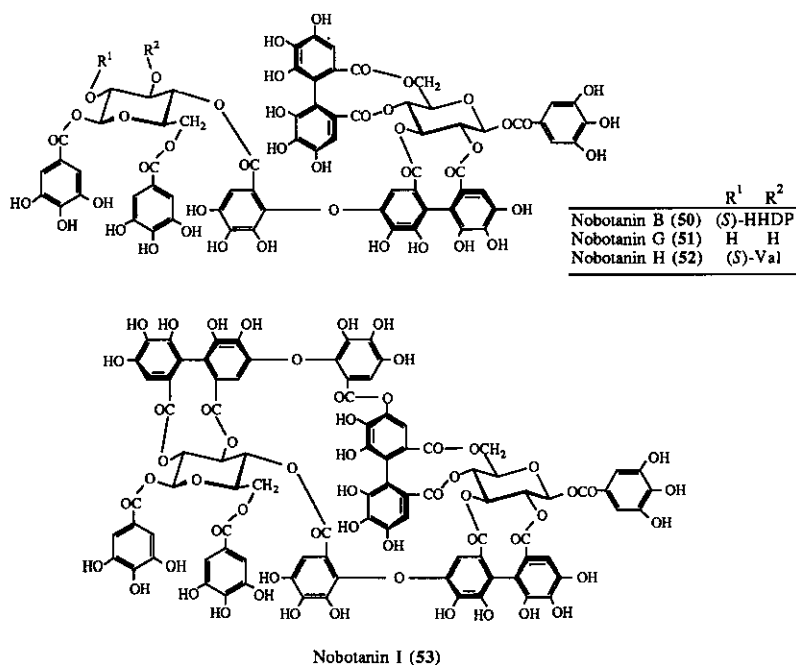
Nobotanins A (44) and F (45),<sup>33</sup> the first members of this group, were isolated from the leaves of Tibouchina semidecandra, and later from several species of Melastomataceous plants. The orientation of the valoneoyl group in these dimers is that of the rugosin-type. This was shown by the production of methylated rugosin C, upon methylation with dimethyl sulfate and potassium carbonate, which induced cleavage of an ester linkage (see Scheme 16). Four other closely related dimers, phillyraeoidins A (46)~D (49)<sup>34</sup> have been obtained from Quercus phillyraeoides, although the orientation of the valoneoyl group in these dimers has not been determined.



Scheme 7

d) Sub-type 4 (Dimers having a valoneoyl group formed by the C-O oxidative coupling between a galloyl group at O-4 in one monomer and an HHDP group at O-2~O-3 of another monomer)

Dimers of this class, nobotanins B (50), G (51), H (52) and I (53),<sup>35,36</sup> were isolated from melastomataceous plants along with nobotanins A and F. Nobotanin I (53) has a labile depside linkage and forms a unique macrocyclic structure, which is easily cleaved to give nobotanin H (52) when kept in an aqueous solution.

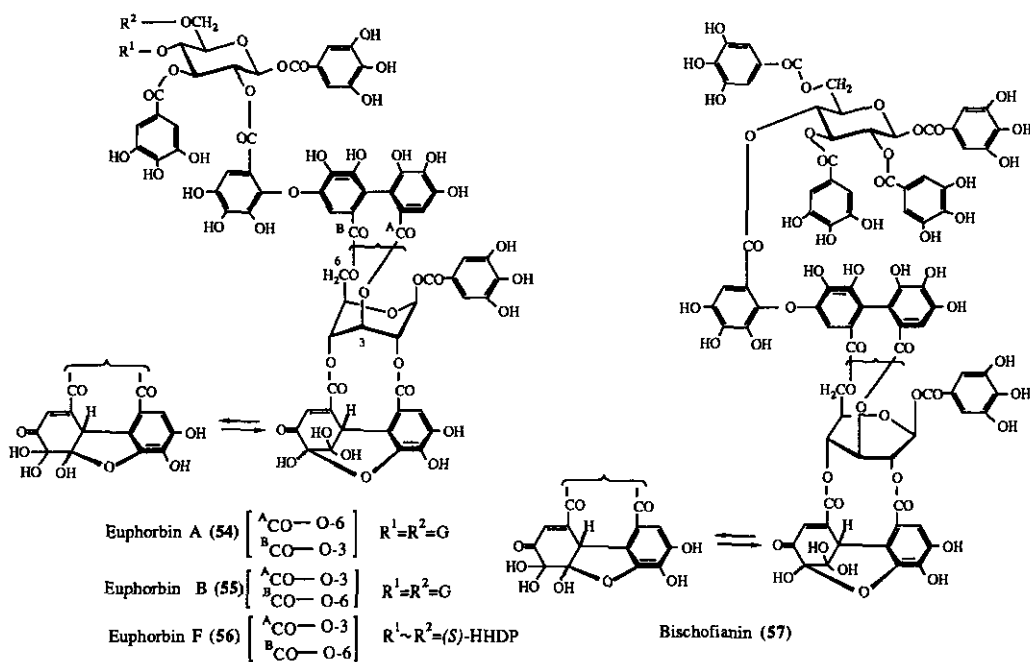


Scheme 8

e) Sub-type 5 (Dimers having a valoneoyl group formed by the C-O oxidative coupling between a galloyl group at O-2 or O-4 in one monomer and an HHDP group at O-3~O-6 of another monomer)

All the dimers mentioned above have <sup>4</sup>C<sub>1</sub> glucopyranose cores, and the HHDP and valoneoyl groups of (S)-configurations. Before the isolation of euphorbins A (54) and B (55)<sup>37</sup> from *Euphorbia hirta*, no oligomer having the (R)-valoneoyl group on the <sup>1</sup>C<sub>4</sub> glucopyranose core was known. Euphorbins A and B are also the first members of the dimers possessing geraniin structure as a part of the molecule. They may be called dimeric dehydroellagitannin because of the presence of DHHDP group in the molecules. Additional congeners are euphorbin F (56)<sup>38</sup> and

bischofianin (57),<sup>39</sup> which were isolated from *E. tirucallii* and *Bischofia javanica*, respectively.



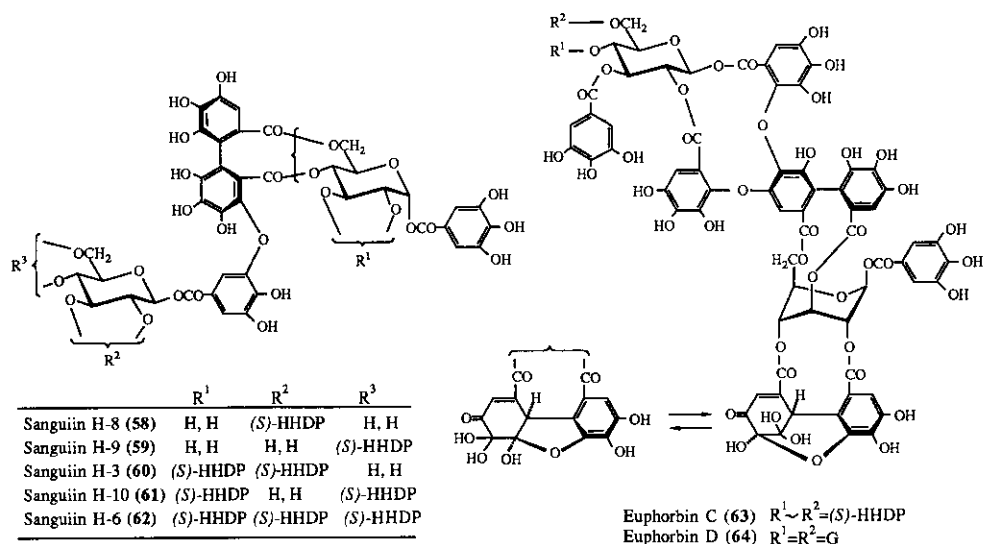
Scheme 9

### Type 3: Dimers with Sanguisorboyl Group (Products of Coupling Mode 3)

A series of sanguins (58)-(62),<sup>40</sup> having a sanguisorboyl group which is isomeric to the valoneoyl group, were obtained from *Sanguisorba officinalis* of Rosaceae. Chromatographic survey has revealed that these dimers are widely distributed in *Rubus* species of the same family as well as *Sanguisorba* species.<sup>41</sup>

### Type 4: Dimers with Euphorbinoyl Group (Products of Coupling mode 4)

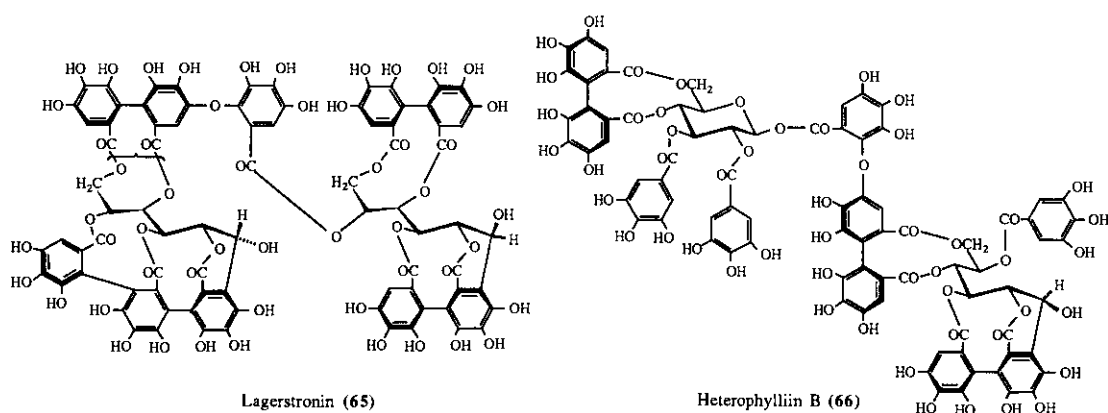
Euphorbins C (63) and D (64),<sup>38</sup> belonging to this group, were isolated from *Euphorbia hirta*. They are biogenetically regarded as related to the dimers of Type-2, sub-type 5. The euphorbinoyl group is regarded to be formed by oxidative coupling between a galloyl group and a valoneoyl group.



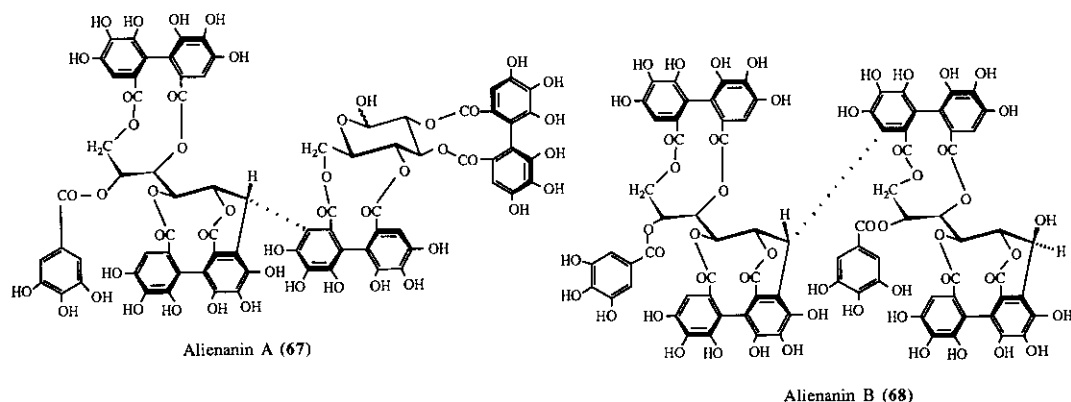
Scheme 10

#### Type 5: Dimers Having C-Glucosidic Monomer

Some dimers having a C-glucosidic tannin monomer (casuarinin and/or stachyurin) in their molecules have recently been reported. The two monomers in lagerstronin (65)<sup>42</sup> and heterophylliin B (66),<sup>43</sup> which were obtained from *Lagerstroemia indica* (Lythraceae) and *Corylus heterophylla* (Betulaceae) respectively, are linked through a C-O bond, whereas those in alienanins A (67) and B (68)<sup>44</sup> isolated from *Quercus aliena* (Fagaceae) are linked by a C-C bond.



Scheme 11

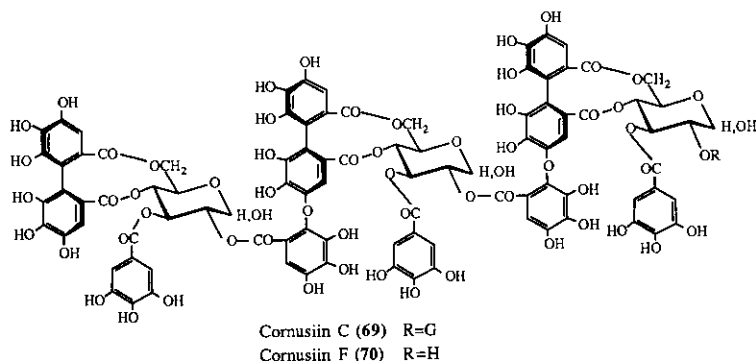


Scheme 12

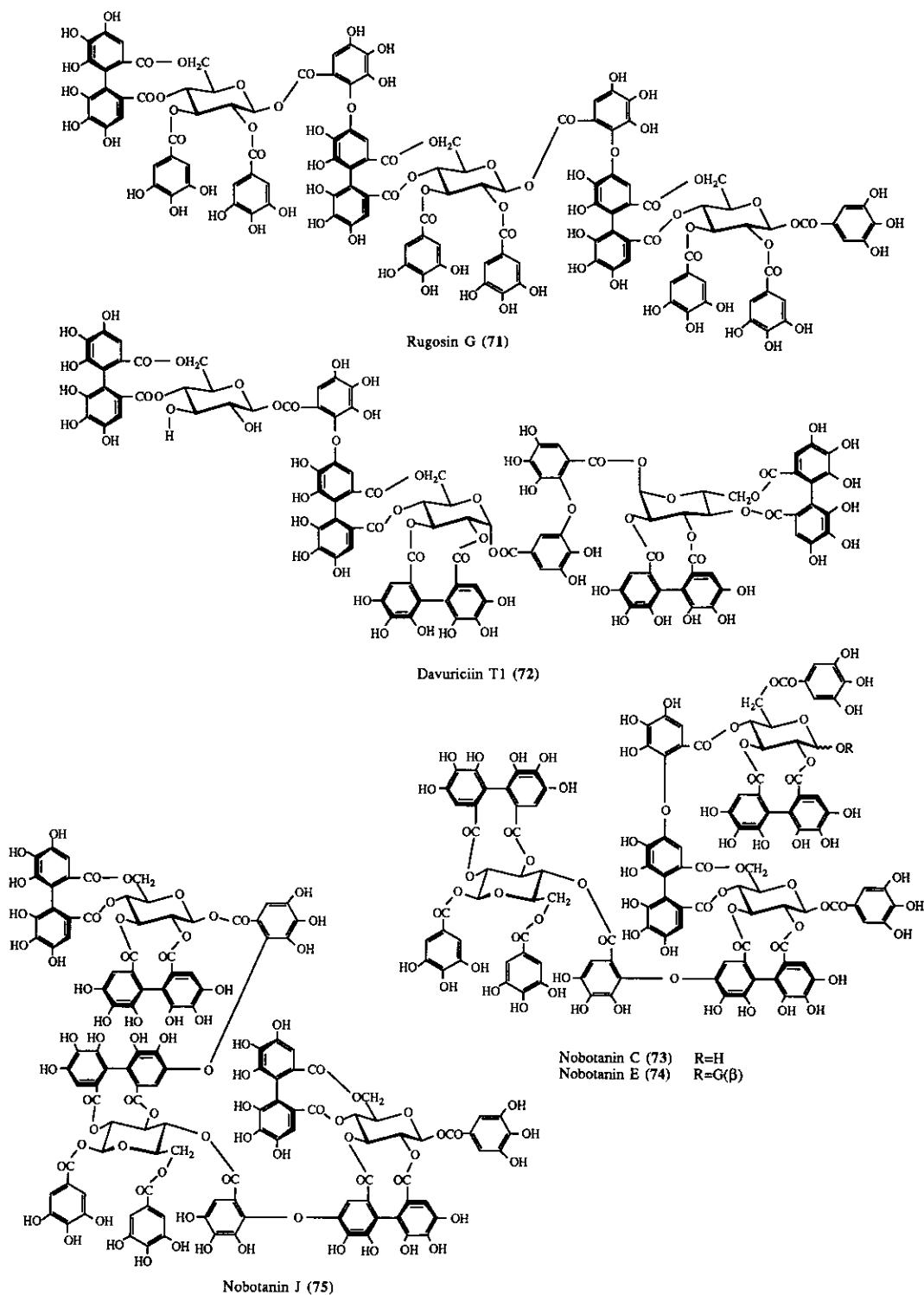
## 2-2. Trimers

Structures of seven trimeric hydrolyzable tannins, which are accompanied by some of dimers such as cornusiins, rugosins, davoriciins and nobotanins in the plants, have been reported.<sup>22, 25, 27, 28, 36</sup> All the trimers, except davoriciin T1, have two valoneoyl groups as connecting units between three monomers, and hence may be classified as Type-2 trimers. Davoriciin T1 (72)<sup>25</sup> is one example of an oligomer having two connecting units that are different from each other (valoneoyl and DHDG groups).

It is noteworthy that cornusiins C (69)<sup>27</sup> and F (70)<sup>28</sup> have a free anomeric hydroxyl group on each glucose core, and form equilibrium mixtures of eight anomers.



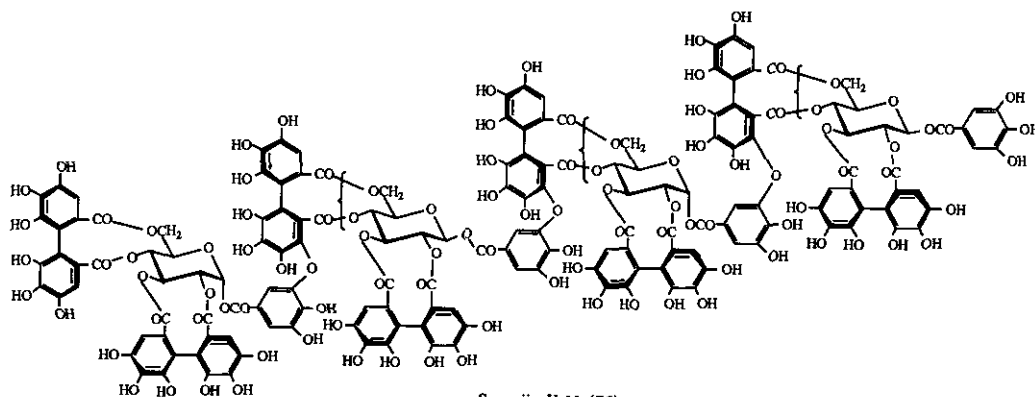
Scheme 13



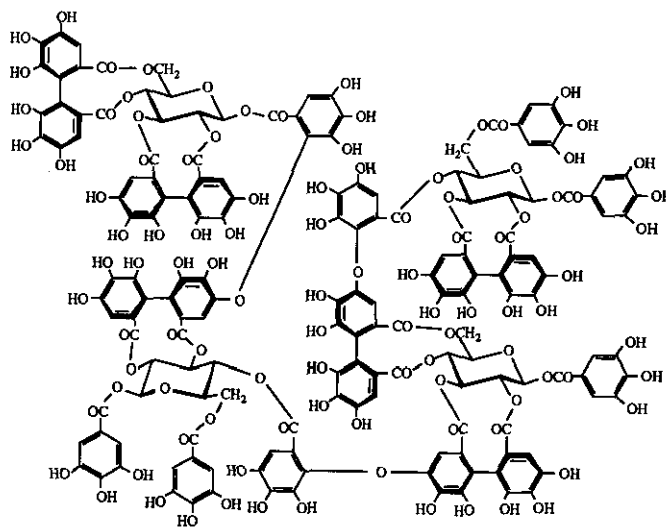
Scheme 14

## 2-3. Tetramers

Two tetramers, sanguin H-11 (76)<sup>40</sup> and nobotanin K (77)<sup>36</sup> have been reported.



Sanguin H-11 (76)



Nobotanin K (77)

Scheme 15

## III. Distribution

In the early stages of research in this area, most oligomeric hydrolyzable tannins were isolated from rosaceous plants. However, oligomers have been found later to be distributed widely in plants of many families, including Cornaceae, Euphorbiaceae, Trapaceae, Nyssaceae, Melastomataceae, Coriariaceae, Betulaceae, Onagraceae, Lythraceae and Fagaceae, accompanied by several monomeric hydrolyzable tannins. The botanical sources of some oligomers that were isolated from several species of plants are summarized in Table 1.

Table 1. Botanical Sources of Oligomeric Hydrolyzable Tannins

| Compound          | Botanical source                 | Reference            |
|-------------------|----------------------------------|----------------------|
| Agrimoniin (3)    | <u>Agrimonia pilosa</u> *        | (9)                  |
|                   | <u>Potentilla kleiniana</u>      | (9)                  |
|                   | <u>Potentilla tormentilla</u>    | (45)                 |
|                   | <u>Rosa laevigata</u>            | Rosaceae (17)        |
|                   | <u>Rosa davurica</u>             | (25)                 |
| Rugosin D (25)    | <u>Rosa rugosa</u> *             | (22)                 |
|                   | <u>Filipendula ulmaria</u>       | (46)                 |
|                   | <u>Coriaria japonica</u>         | Coriariaceae (21)    |
|                   | <u>Trapa bicornis</u>            | Trapaceae (47)       |
|                   | <u>Euphorbia prostrata</u>       | Euphorbiaceae (38)   |
| Rugosin E (27)    | <u>Rosa rugosa</u> *             | Rosaceae (22)        |
|                   | <u>Coriaria japonica</u>         | Coriariaceae (21)    |
|                   | <u>Euphorbia prostrata</u>       | Euphorbiaceae (38)   |
| Rugosin F (28)    | <u>Rosa rugosa</u> *             | Rosaceae (22)        |
|                   | <u>Stachyurus praecox</u>        | Stachyuraceae (48)   |
|                   | <u>Corylus heterophylla</u>      | Betulaceae (43)      |
| Oenothlein B (41) | <u>Oenothera erythrosepala</u> * | Onagraceae (15)      |
|                   | <u>Lythrum anceps</u>            | Lythraceae (49)      |
|                   | <u>Woodfordia fruticosa</u>      |                      |
| Cornusiin A (33)  | <u>Cornus officinalis</u> *      | Cornaceae (27)       |
| Cornusiin C (69)  | <u>Camptotheca acuminata</u>     | Nyssaceae (29)       |
|                   | <u>Trapa bicornis</u>            | Trapaceae (47)       |
| Camptothin A (36) | <u>Camptotheca acuminata</u> *   | Nyssaceae (29)       |
|                   | <u>Cornus officinalis</u>        | Cornaceae (27)       |
| Nobotanin B (50)  | <u>Tibouchina semidecandra</u> * | (36)                 |
|                   | <u>Hetrocentron roseum</u>       | Melastomataceae (36) |
|                   | <u>Schizocentron elegans</u>     |                      |
| Sanguin H-6 (62)  | <u>Sanguisorba officinalis</u> * | Rosaceae (40)        |
|                   | <u>Rubus spp.</u>                | (41). (14)           |

\*Plant species from which each oligomer was originally isolated.

#### IV. Analysis of Oligomeric Hydrolyzable Tannins

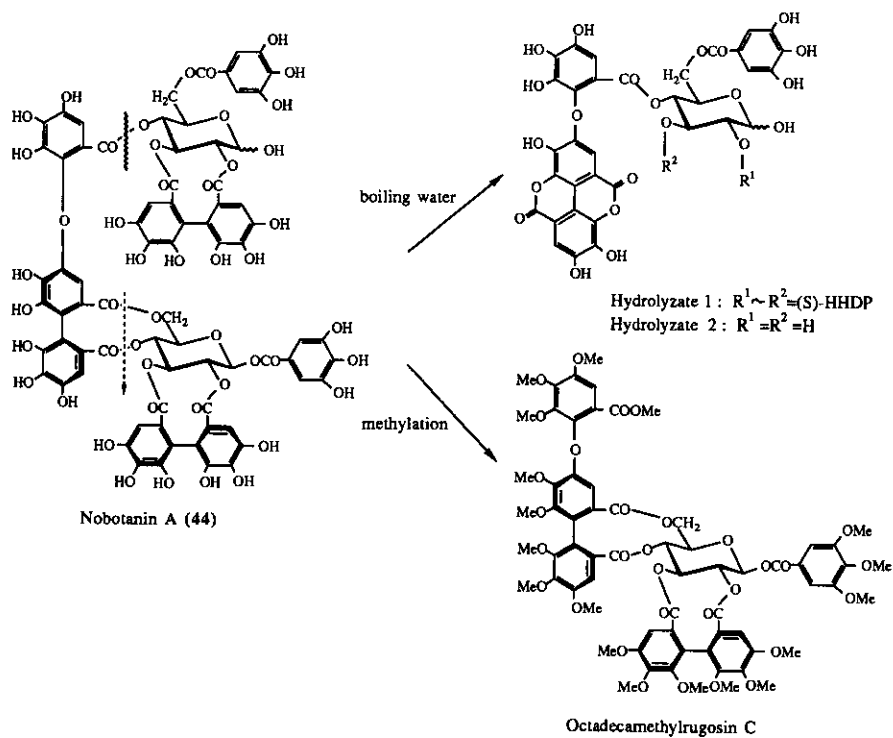
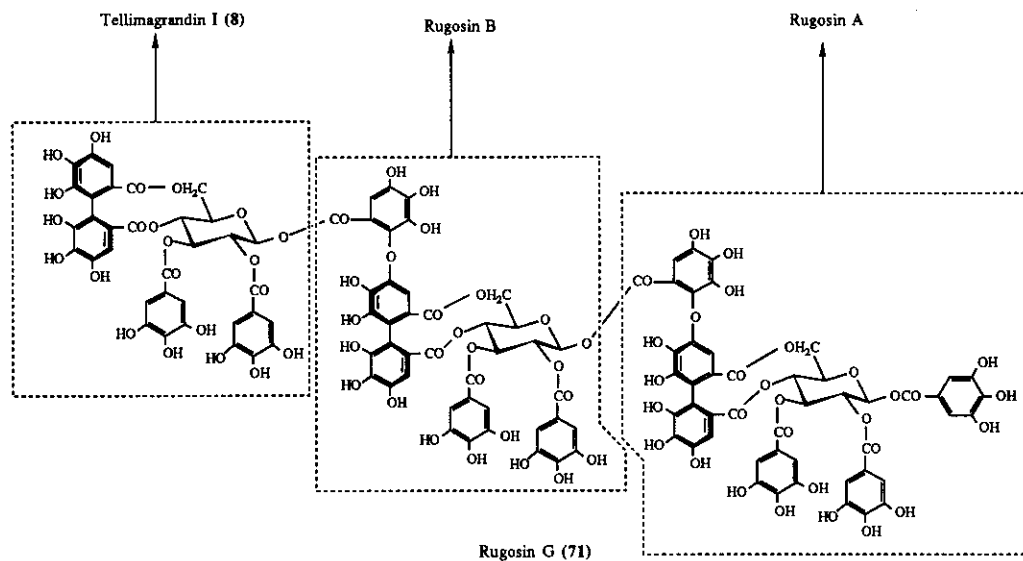
Oligomeric hydrolyzable tannins are generally more polar and unstable than the monomers, and are generally more sensitive to heat.<sup>1</sup> The cautions for extraction of tannins from plant materials should be strictly applied to oligomeric hydrolyzable tannins. These cautions require extraction at temperature not higher than room temperature, and use of suitable solvents for extracting tannins which may be bound to some other materials in the plant tissues.

Oligomers in plant extracts can be differentiated from the monomers by normal-phase hplc which gives peaks of longer retention time for larger oligomers.<sup>1</sup> Although hplc on the GPC column gives approximate molecular weight of oligomers, the normal-phase hplc is a convenient method for monitoring oligomers in the complex mixtures of tannins being fractionated.

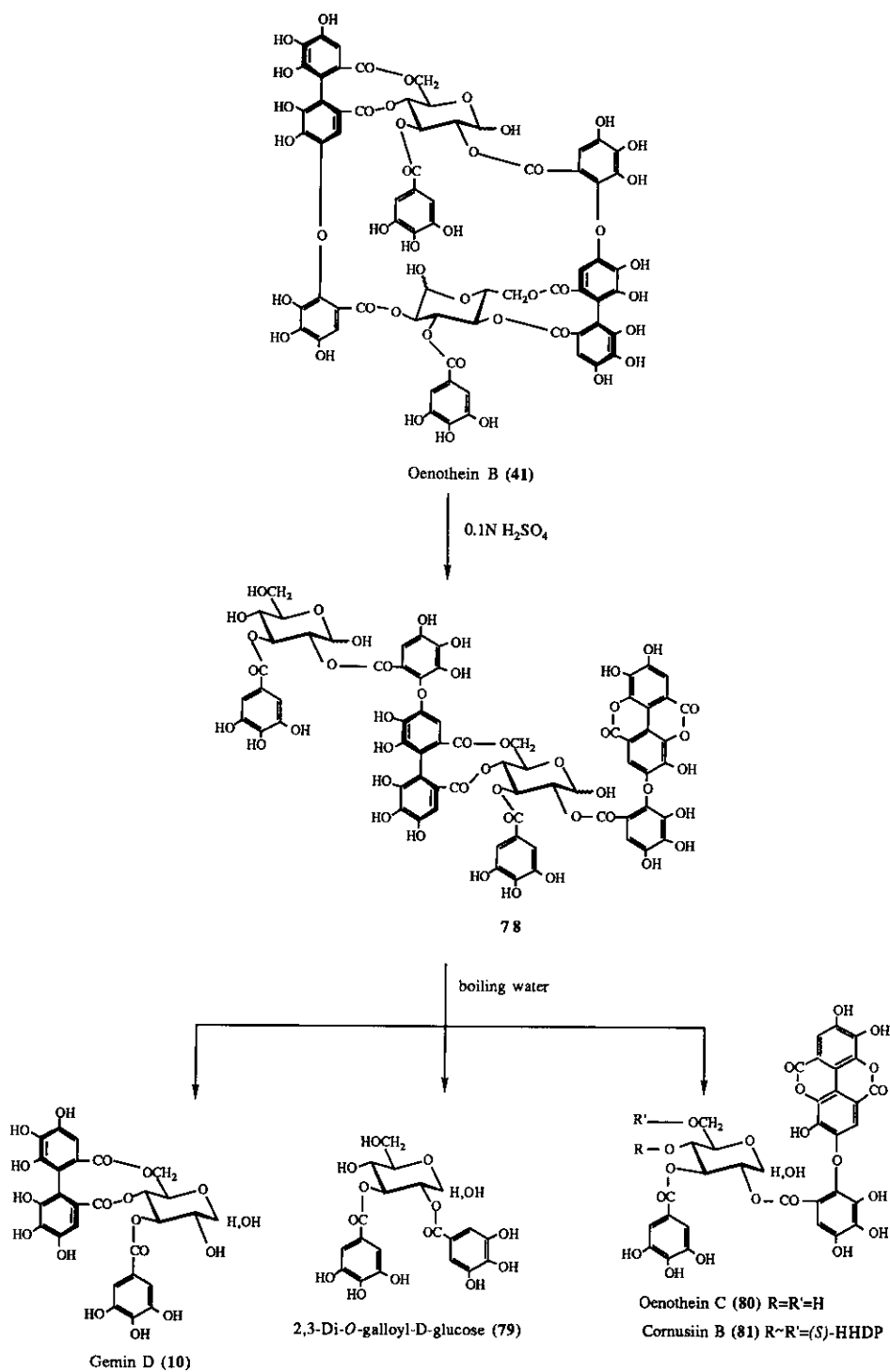
Since the oligomers are also apt to bind with various substances, such as proteins and polysaccharides,<sup>1</sup> and to be hydrolyzed during chromatographic separation, careful selection of appropriate solid supports and solvent systems is required for chromatographic separation. Combination of counter-current chromatography such as recently developed centrifugal partition chromatography (CPC), and column chromatography over Sephadex LH-20, Toyopearl HW-40 (coarse, fine and superfine grades) and other resins, usually leads to successful purification.<sup>49</sup> Application of these techniques to labile oligomeric hydrolyzable tannins has been reviewed recently.<sup>1,50</sup>

#### V. Structure Elucidation

Structure determination of oligomeric hydrolyzable tannins has been facilitated very much by a stepwise approach, which is based on chemical degradation and spectroscopy of the products, to firmly establish their structures. It usually starts with complete acid hydrolysis of each oligomer, likewise in the structure elucidation of monomeric hydrolyzable tannins, to recognize the component units (polyphenolic acids and sugars). Much information concerning molecular weight, and number of component units and their binding sites on the sugar cores, is provided by spectroscopic methods. These methods include those of FAB-ms and nmr spectroscopy, among which various 2D nmr techniques are particularly useful. Application of these techniques to the oligomers has also been reviewed recently.<sup>1</sup>



Scheme 16



Scheme 17

In addition to these methods, partial hydrolysis combined with methylation is required for the establishment of a complex structure. Partial hydrolysis in boiling water or dilute sulfuric acid, monitored by hplc often produces as the hydrolysates, monomeric hydrolyzable tannins of the structures mostly known. The valoneoyl group in a molecule of oligomers belonging to Type 2-a is often hydrolyzed preferentially at the ester bond on the galloyl moiety, to afford a monomer in which the ester bonds on the HHDP moiety of the valoneoyl group are retained. For example, rugosin G (71), a trimeric hydrolyzable tannin, is easily hydrolyzed in boiling water within 30 min. to yield tellimagrandin I (8), rugosin B and rugosin A in a ratio of 1:1:1.<sup>22</sup> (Scheme 16). On the other hand, the valoneoyl group in dimers of Types 2-b~e is often partially hydrolyzed at the two ester linkages on the HHDP moiety, to yield a monomer retaining the ester bond on the galloyl moiety of the valoneoyl group. Prolonged methylation of oligomers with dimethyl sulfate and potassium carbonate in dry acetone often provides a partially degraded monomeric methyl derivative, accompanied by the permethylated derivative. This monomeric product is generally formed by cleavage of the ester bond on the galloyl part of the valoneoyl group, regardless of its location in a molecule, as exemplified by methylation of nobotanin A (44)(Scheme 16). Structures of the oligomers hitherto isolated have been generally confirmed by combination of these methods. However, it is noteworthy that the ether bond of valoneoyl group in a molecule is sometimes cleaved upon partial hydrolysis to give monomers, as illustrated by the hydrolysis of oenothain B (41) (Scheme 17).<sup>15</sup> Similar cleavage of valoneoyl group in the oligomers was observed upon partial hydrolyses of isorugosin D (26)<sup>23</sup> and euphorbin A (54),<sup>37</sup> in boiling water or dilute sulfuric acid.

#### VI Biological Activities of Oligomeric Hydrolyzable Tannins

The binding activities of tannins represented by the RA and RMB values<sup>51</sup> are generally intensified with increase in molecular weight up to about 1000, and this increase is not observed at molecular weights above 1000.<sup>1,51</sup> However, the increase for these tannins is evident when the RA and RMB values are recalculated based on molar concentration.<sup>1</sup> This means that the biological activity of oligomeric hydrolyzable tannins, as far as they are based on the binding activities of tannins, may not differ much from those of monomeric hydrolyzable tannins of molecular weight near 1000. However, several biological activities were exhibited

almost solely by the oligomers, or were exhibited by them more than by monomers. Examples of such activities are the host-mediated anti-tumor activity of several oligomers such as ceneohein B (referred in II-1), corrianin A and agrimonin, etc.,<sup>11</sup> and the anti-HIV activity of some of these oligomers.<sup>31</sup>

#### VII. Conclusion

While the chemistry of hydrolyzable tannins had been limited to the monomers in the years up to 1981, the isolation and the structure determination of oligomers, initiated by those of agrimonin, showed that this new field of research is unexpectedly large. They are widely distributed among plants, and each oligomer has been obtained as a pure compound of well-defined structure, contributing extensively to change of the old concept of tannin.<sup>1,13</sup> Further developments in the research of oligomeric hydrolyzable tannins are expected not only in the study of their chemical structures and distribution in plants, but also in studies related to the significance of their presence, to the chemotaxonomy and plant evolution, and to the biological activity associated with the traditional use of medicinal plants containing them as well as new medical applications.

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