Natural Products

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Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis**

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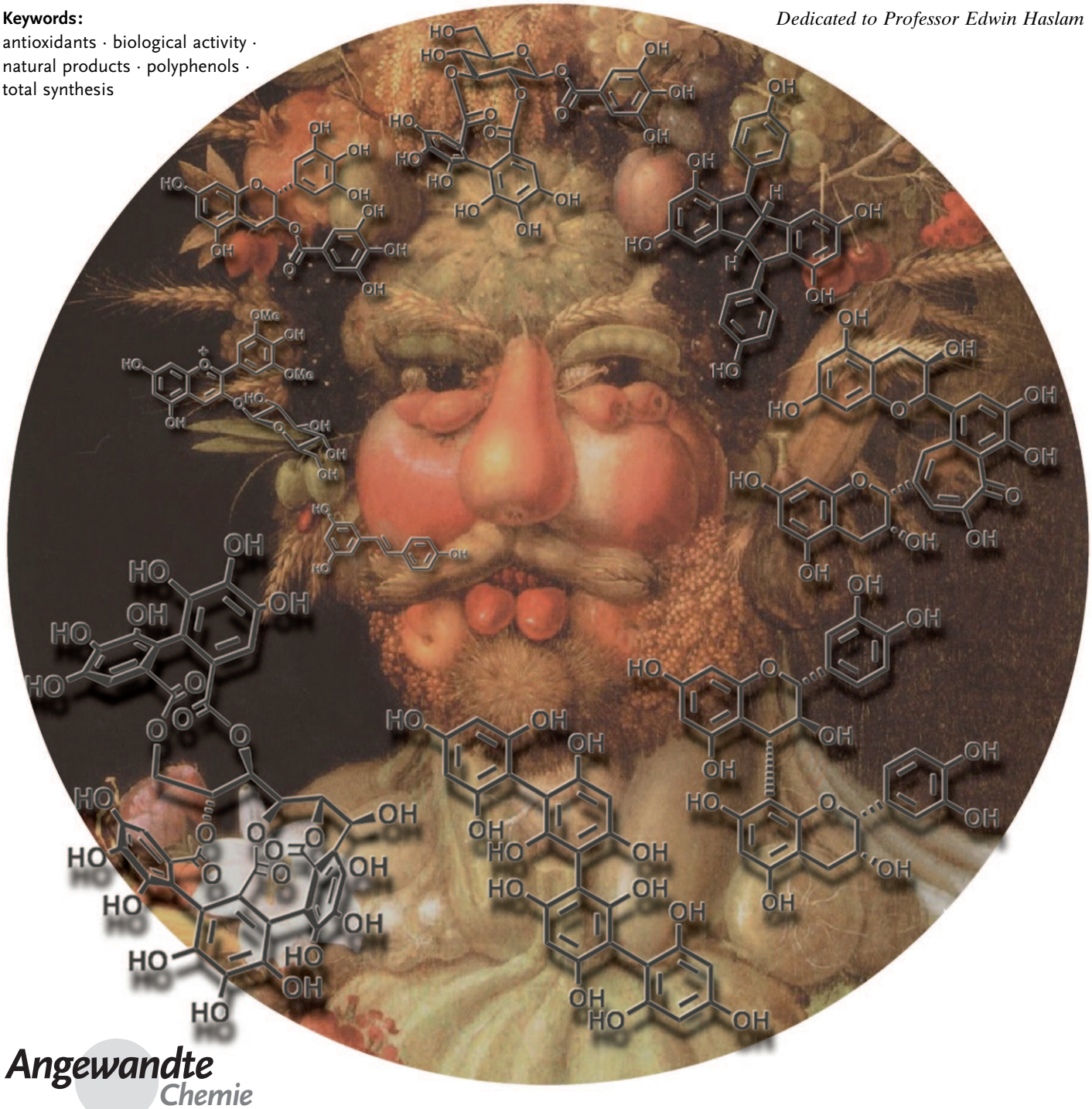
Dedicated to Professor Edwin Haslam



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Eating five servings of fruits and vegetables per day! This is what is highly recommended and heavily advertised nowadays to the general public to stay fit and healthy! Drinking green tea on a regular basis, eating chocolate from time to time, as well as savoring a couple of glasses of red wine per day have been claimed to increase life expectancy even further! Why? The answer is in fact still under scientific scrutiny, but a particular class of compounds naturally occurring in fruits and vegetables is considered to be crucial for the expression of such human health benefits: the polyphenols! What are these plant products really? What are their physicochemical properties? How do they express their biological activity? Are they really valuable for disease prevention? Can they be used to develop new pharmaceutical drugs? What recent progress has been made toward their preparation by organic synthesis? This Review gives answers from a chemical perspective, summarizes the state of the art, and highlights the most significant advances in the field of polyphenol research.

From the Contents

> *"The same wine, either because it will have changed itself, or because our body will have changed, can taste sweet at such a time, and, at such another time, bitter ..."*
> Aristotle, Metaphysics
> From the French translation by Jean Tricot **1933**, tome 1, Γ, 5, p. 146 (Librairie Philosophique J. Vrin, 1991)

1. A Little Bit of History

Before being called polyphenols, these plant-derived natural products were globally referred to as "vegetable tannins" as a consequence of the use of various plant extracts containing them in the conversion of animal skins into leather. The origins of this leather-making process get lost in the depths of the most ancient records of the history of human civilizations, but literature sources seem to agree that the Ancient Greeks of the archaic period (ca. 800–500 BC) were the first in Europe to develop the technology by relying on the use of oak galls.[1] The first mentions of vegetable tanning in the classical literature are accredited to Theophrastus of Eressus (371–286 BC), the acclaimed founder of the science of botany, in his *Historia Plantarum* plant encyclopedia. Over the centuries, "vegetable tannins" have never ceased to garner general (and commercial) interest, as well as scientific curiosity,[2] and the development of the leather industry as a source of raw materials for the manufacture of not only various commodity products but also of numerous heavy leather-made articles that equipped armed forces in times of war clearly had something to do with such a continuous infatuation. In the first half of the 20th century, one of the main sources of natural tanning materials was the quebracho heartwood, produced at the time almost exclusively on a large scale in Argentina and Paraguay. During this tormented period of history, belligerant nations engaged in sustained efforts to find a substitute to quebracho extracts. For example, the German leather industry developed the production of tanning materials from oak trees growing in the south of the country, and hence, gradually became independent from the importation of quebracho from South America by the time of the Second World War.[3]

It will certainly not come as a surprise that chemists got involved in this "vegetable tannins" affair. The International Association of Leather Trades Chemists was founded in London in 1897, and is still active today under the name of the Society of Leather Technologists and Chemists. The American Leather Chemists Association was founded in 1903, and is also still active today. This association banded together chemists mainly concerned with finding an accurate method for analyzing tanning extracts used in the leather industry. This was indeed a valuable and quite honorable objective, but far from trivial given the means of chemical analysis available at the time. Even the determination of the polyphenolic nature of "vegetable tannins" was not a simple matter, and it was further complicated by the variety of plant sources containing tanning materials of different chemical compositions. Considerable efforts were thus devoted from the

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[**] The background of the frontispiece is one of the masterpieces of Giuseppe Arcimboldo (Italian painter, 1527–1593) which shows a portrait of Rudolf II (Holy Roman Emperor, House of Habsburg) as Vertumnus (roman god of seasons, plant growth, garden, and fruit trees) made entirely of fruits, vegetables, and flowers.

beginning of the 20th century onwards to the study of the chemistry of tanning plant extracts in an attempt to tackle the structural characterization of their polyphenolic constituents. Even the tenacity and major contributions of the German Nobel Laureate Emil Fischer and those of several of his disciples, such as Karl Freudenberg[4] only unveiled the complexity of the problem and fell short of placing research on "vegetable polyphenols" as a priority theme in analytical organic chemistry. The lack of high-performance analytical tools in these early days is certainly a reason for the shortfall of knowledge on complex polyphenols at the molecular level and, consequently, for the unfortunate absence of better recognition of the topic by chemists. This regrettable situation has without question improved greatly today, but is still in some respects unchanged, as the study of plant polyphenols still remains a special and rather exotic topic in modern organic chemistry.

Fortunately, over the years, botanists, plant physiologists, phytochemists, and biochemists, as well as a few obstinate organic chemists, kept on studying polyphenols and underlying their significance not only as major and ubiquitous plant secondary metabolites, but also as compounds that express properties with numerous implications and potential exploitations in various domains of general public and commercial interests. During the second half of the 20th century, research on polyphenols started to address objectives beyond those related to leather manufacture. The first glimpses of a definition of "plant polyphenols" can, however, be found in the scientific literature pertaining to this ancestral utilization of polyphenolic plant extracts. In 1957 Theodore White, an industrial chemist who worked for the British corporation, The Forestal Land, Timber and Railway, Ltd., a major player in the aforementioned quebracho extract industry, pointed out that the term "tannin" should strictly refer to plant polyphenolic materials having molecular masses between 500 and 3000 Da and a sufficiently large number of phenolic groups to be capable of forming hydrogen-bonded cross-linked structures with collagen molecules (the act of tanning). White was also among the first chemists to stress that many simpler plant (poly)phenolic substances such as gallic acid and catechin, which give some of the diagnostic reactions of phenolic compounds—such as formation of intense blue-black complexes upon treatment with iron(III) salts and oxidation with permanganate—do not cross-link collagen, and hence have no tanning action, even though they are adsorbed by animal skin and can precipitate gelatin, the hydrolytically and thermally denaturated form of collagen.[2,5] In brief, all vegetable tannins are polyphenolics, but the reciprocal is not necessarily true.

Stéphane Quideau received his PhD in 1994 with Prof. J. Ralph from the University of Wisconsin-Madison. After postdoctoral research at The Pennsylvania State University with Prof. K. S. Feldman, he moved to Texas Tech University as an Assistant Professor. In 1999, he moved to the University of Bordeaux, and joined the European Institute of Chemistry and Biology in 2003. After being nominated as junior member of the "Institut Universitaire de France" in 2004, he was promoted to Full Professor in 2005. In 2008 he received the Scientific Prize of the "Groupe Polyphénols" society, and was elected President of this society.

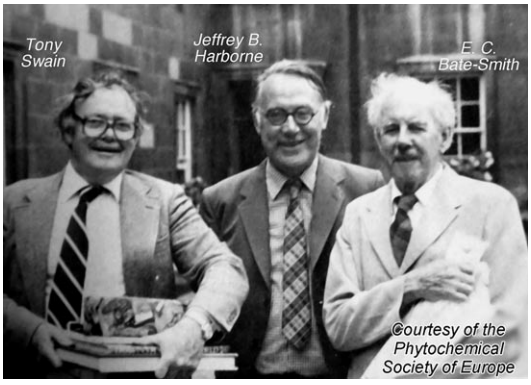
Denis Deffieux received his PhD in 1993 with Prof. C. Biran from the University of Bordeaux for his work on the electrochemical silylation of polyhalogenated aromatic compounds. He then joined the group of Prof. George Olah in Los Angeles as a postdoctoral fellow. In 1996, he moved back to Bordeaux as Maître de Conférences in Organic Chemistry at the University of Bordeaux, and joined Prof. Stéphane Quideau's group in 1999. His research interests include the total synthesis of polyphenols and the elucidation of the biosynthesis of flavanoids.

Céline Douat-Casassus received her PhD in 2001 with Dr. J.-A. Fehrentz in Prof. J. Martinez's group in Montpellier for her work on solid-phase synthesis of lipopeptides. She then joined the group of Prof. J.-L. Reymond's at Bern University, where she contributed to the development of catalytic peptide dendrimers. In 2004, she moved to Bordeaux to Prof. S. Quideau's group, where she worked on the synthesis of antigenic peptidomimetics. Since 2007, she has been a CNRS researcher in the group. Her research interests include the solid-phase synthesis of polyphenolic ellagitannin derivatives.

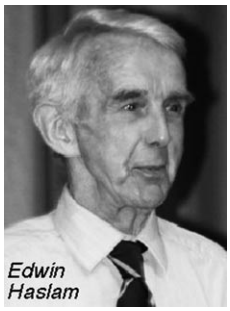
Laurent Pouységu studied chemistry at the University of Bordeaux, and received his PhD in 1997 with Prof. B. De Jéso for his work on carbohydrate chemistry. He then joined Prof. S. Quideau's group as a postdoctoral fellow at Texas Tech University, where he worked on the chemistry of ortho-quinol acetates. In 1998, he moved back to Bordeaux as Maître de Conférences in Organic Chemistry in Prof. Quideau's group. His research interests include hypervalent iodine chemistry and the oxidative dearomatization of phenols for the total synthesis of plant polyphenols, alkaloids, terpenoids, and polyketides.

Unfortunately, the term "tannin" has very often been used to indicate plant phenolics on the sole basis of positive responses obtained from the aforementioned diagnostic tests, irrespective of the number of phenolic groups, structural construction (monomeric or oligo/polymeric), or tanning capacity. This failure to appreciate the distinctive characteristics of polyphenolic vegetable tannins, as opposed to simple plant phenols, has inevitably led to some confusion in the literature concerning not only the definition of "plant polyphenols", whether synonymous or not with "vegetable tannins", but also the role that plant phenolics, and polyphenols in particular, may play in a number of fields.[6] As alluded to above, after the Second World War, polyphenols gradually became a topic of intensive investigation in various plant-related scientific domains, including applied research areas such as agriculture, ecology, food science and nutrition, as well as medicine.[6,7] The development of more and more advanced analytical techniques that paralleled this gradual expansion of interest in polyphenol research during the second half of the past century clearly had a major positive impact on both the development of the field and its appreciation by the scientific community at large.

We believe credit is mainly due to three scientists who managed to open the door to both our basic and applied knowledge of plant polyphenols today. The first two are the British phytochemists E. C. Bate-Smith and Tony Swain, who



carried out numerous seminal investigations on various plant phenolics from the early 1950s to the late 1980s.[8] In 1957, at the University of Cambridge, they co-founded the "Plant Phenolics Group", the forerunner of the Phytochemical Society of Europe that they co-founded 20 years later together with Jeffrey B. Harborne, another eminent British scientist in the field of phytochemistry and a flavonoid specialist. In 1961, they co-founded the journal *Phytochemistry*.[9] In 1962, Bate-Smith and Swain came up with their own proposal for a definition of plant polyphenols as "*water-soluble phenolic compounds having molecular weights between 500 and 3000 (Da) and, besides giving the usual phenolic reactions, they have special properties such as the ability to precipitate alkaloids, gelatin and other proteins from solution*".[10] This definition was in fact only a slight variation of White's earlier proposal, but the collagen-specific tanning action proviso was no longer specifically stated.



This definition was later refined at the molecular level by the third scientist to whom we should give credit for his outstanding achievements in the field. We are referring here to Edwin Haslam, a British physical-organic chemist at the University of Sheffield, who dedicated his career to the study of many if not all aspects of polyphenol science, including chemical reactivity and synthesis, as well as biochemical and biophysical investigations on various classes of polyphenols, particularly their molecular interactions with other biomolecules such as proteins and polysaccharides. Haslam expanded the definitions of those of Bate-Smith, Swain, and White such that the term "polyphenols" should be used as a descriptor for water-soluble plant phenolic compounds having molecular masses ranging from 500 to 3000–4000 Da and possessing 12 to 16 phenolic hydroxy groups on five to seven aromatic rings per 1000 Da of relative molecular mass. Furthermore, the compounds should undergo the usual phenolic reactions and have the ability to precipitate some alkaloids, gelatin, and other proteins from solution.[11] Again, the capacity of plant phenolics to exhibit a tanning action on skin collagen molecules is not retained as an essential condition to qualify them as polyphenols, but the use of the term "polyphenols" as a synonym for "vegetable tannins" has regrettably persisted in the literature. Some might still argue that the structural criteria of this definition make it too strict, leaving out many plant phenolics capable of expressing, at least to some extent, some of the properties and chemical reactivities of those fully fitting the definition. This view would, however, miss the fact that the focal criterion from which White, Bate-Smith, Swain, and Haslam (WBSSH) originally based their classification of plant phenolics as "polyphenols" or not was first and foremost the capacity to engage in complexation with other biomolecules. This quintessential property of polyphenols underlies many of the roles they can play as secondary metabolites in plants as part of their chemical defence, as well as some of their characteristic effects in numerous practical applications, such as in herbal medicines, in plant-derived foodstuffs and beverages, in floral pigmentation, and—even still today—in the manufacture of leather.[6]

Nowadays, plant polyphenols enjoy an ever-increasing recognition not only by the scientific community but also, and most remarkably, by the general public because of their presence and abundance in fruits, seeds, vegetables, and derived foodstuffs and beverages, whose regular consumption has been claimed to be beneficial for human health. It is their capacity to scavenge oxidatively generated free radicals, such as those derived from lipids and nucleic acids, that has often been highlighted as the fundamental chemical event that underlies their utility in reducing the risk of certain age-related degenerations and diseases. Although this so-called antioxidation property is not listed among the qualifying factors that make a plant phenolic a "true" polyphenol according to the WBSSH definition, it has become the

trademark of "polyphenols" in recent exploitations by the agro-food, cosmetic, and parapharmaceutic industries. However, antioxidation is not a property limited to polyphenols, as numerous simple plant phenols are strong antioxidants, with many of them being in fact used as the active principles present in some industrial formulations. The use of the term "plant phenols" by industry would definitely be more appropriate, but the term "polyphenols" is preferred for commercial communications. As in the case of earlier confusions surrounding the use of the term "tannins" in the scientific literature, the term "polyphenols" has been and is still often misused by scientists from industry as well as academia. The classical WBSSH definition tends to be disregarded, if not completely forgotten, and alternative meanings of the word "polyphenol" have unfortunately emerged. However, one cannot be totally disappointed by this situation, for it clearly shows the growing interest that plant (poly)phenolics generate today in various scientific fields, while perhaps also hinting at a need for a new and comprehensive, yet scientifically sound, definition of "polyphenols".

2. What Are Plant Polyphenols Really?

A strict interpretation of the WBSSH definition leads to the conclusion that only substances bearing a large enough number of di- and/or trihydroxyphenyl units, by virtue of either their oligomeric nature or the multiple display of these phenolic motifs in their monomeric forms, can fit the definition as long as they remain soluble in water. This would mean, for example, that even poly(hydroxyphenylpropanoid)-based lignin polymers are not "polyphenols"! In his excellent 1998 reference book entitled "*Practical Polyphenolics*",[6] Haslam recognized only three classes of polyhydroxyphenyl-containing natural products that conform to the restrictions implied by the WBSSH definition.

2.1. Three Classes of Plant Polyphenols and More ...

These three classes of "true" polyphenols are 1) the proanthocyanidins (condensed tannins) such as procyanidins, prodelphinidins, and profisetinidins (Figure 1), which are derived from the oligomerization of flavan-3-ol units such as (epi)catechin, epigallocatechin, and fisetinidol (see Figure 7),[12] 2) the gallo- and ellagitannins (hydrolyzable tannins), which are derived from the metabolism of the shikimate-derived gallic acid (3,4,5-trihydroxybenzoic acid) that leads through esterification and phenolic oxidative coupling reactions to numerous (near 1000) monomeric and oligomeric polyphenolic galloyl ester derivatives of sugar-type polyols, mainly D-glucose (Figure 2),[11,13] and 3) the phlorotannins that are found in red-brown algae (Figure 3) and essentially derived from the oligomerizing dehydrogenative coupling of phloroglucinol (1,3,5-trihydroxybenzene; Figure 10).[14]

These three classes of polyphenols are all qualified by the term "tannin". This term comes from the French word "tan"

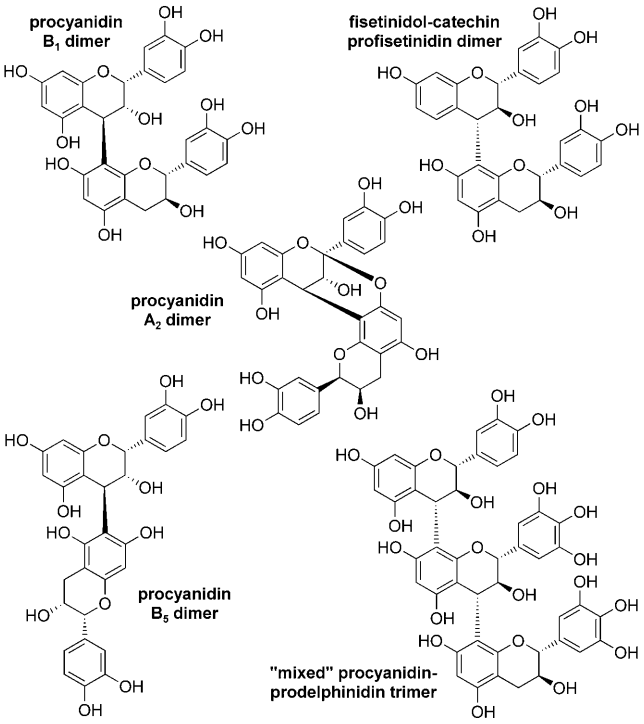


Figure 1. Representative examples of condensed tannins.

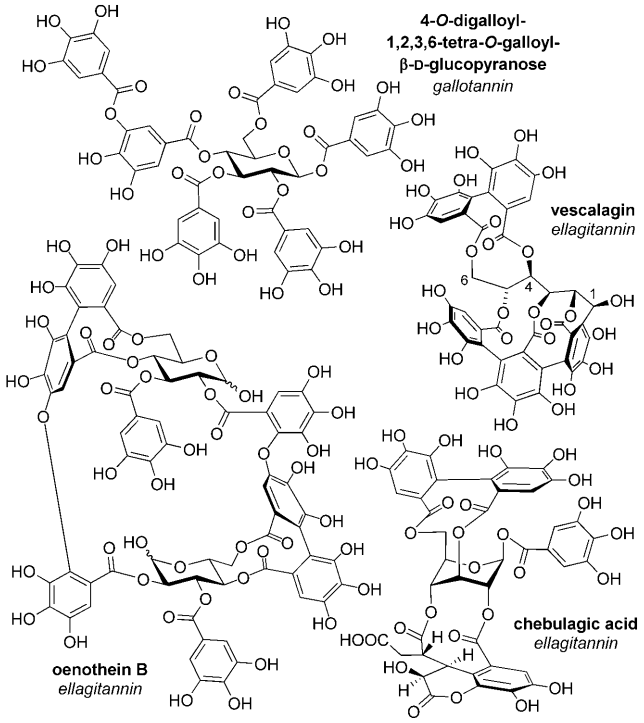


Figure 2. Representative examples of hydrolyzable tannins.

(powdered oak bark extracts traditionally used in the making of leather), which is itself etymologically derived from the ancient keltic lexical root "tann-" meaning oak. The capacity of both condensed and hydrolyzable tannins to tan animal skins into leather has been amply proven, but not that of the

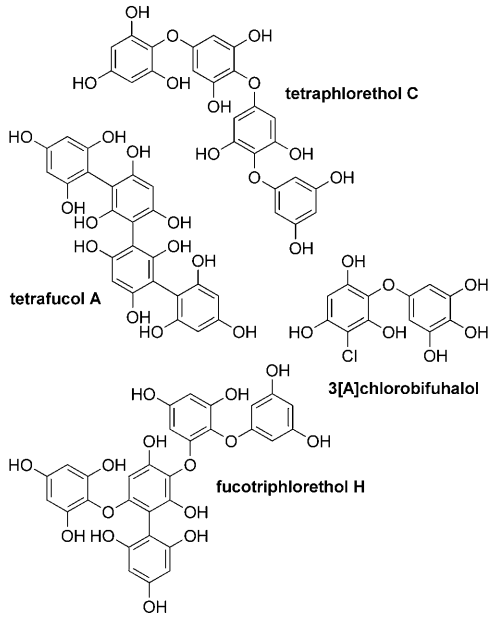


Figure 3. Representative examples of phlorotannins.

phlorotannins. Several other groups of more or less complex plant phenolics, to which the term "tannin" has also been attributed without any firm evidence of their tanning action, could nevertheless be considered as "true" polyphenols, as they fit to a large extent the WBSSH definition. For example, flavanols occurring in green tea (such as epicatechin gallate (ECG) and epigallocatechin gallate (EGCG); Figure 7) give rise through oxidative transformations to the tropolone-containing dimeric theaflavins and complex oligo/polymeric thearubigins of black tea. The two product groups are globally referred to as theatannins (Figure 4).[15]

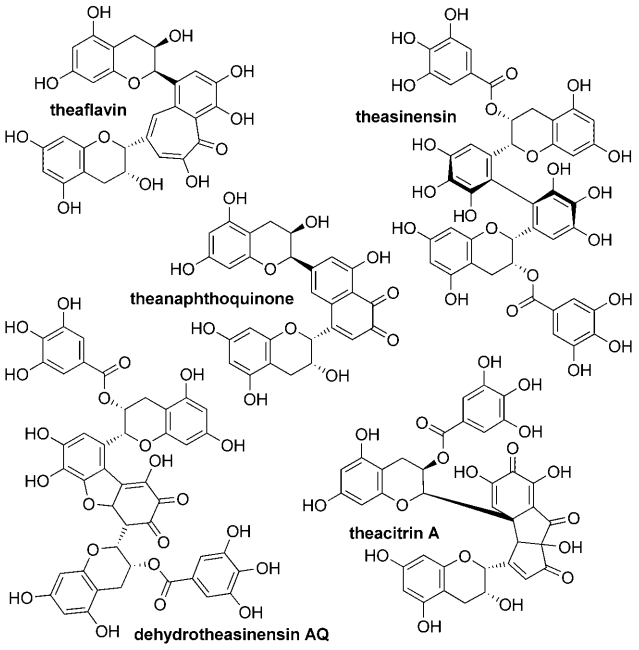


Figure 4. Representative examples of theatannins.

The general plant metabolism of phenylpropanoids furnishes a series of hydroxycinnamic acids (C_6-C_3) that differ from one another by the number of hydroxy and methoxy groups on their phenyl unit (*p*-coumaric acid, ferulic acid, sinapic acid, caffeic acid). These monophenolic carboxylic acids are often found esterified to polyols. One of these acids, caffeic acid (3,4-dihydroxycinnamic acid; Figure 10), is encountered in medium-sized polyester derivatives of the tetraolic quinic acid, such as 3,5-di-*O*-caffeoylquinic acid, found in coffee beans, for example.[16] These derivatives are known as the chlorogenic acids, and are globally referred to as caffetannins (Figure 5).[14c,16b] In fact, numerous polyols,

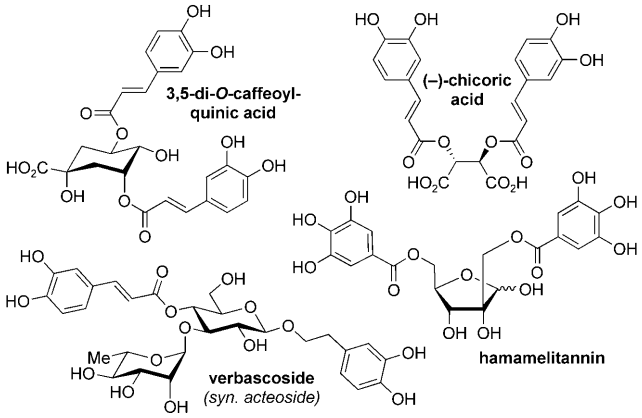


Figure 5. Representative examples of polyphenolic caffeoyl ester derivatives, including the caffetannin 3,5-di-*O*-caffeoylquinic acid, and structure of the polyphenolic galloyl ester derivative hamamelitannin.

including saccharides, are acylated, in much the same way as in gallo- and ellagitannins, by polyhydroxyphenylcarbonoyl residues, among which the most common units are the caffeoyl (C_6-C_3), the galloyl (C_6-C_1), and its dehydrodimeric hexahydroxydiphenoyl (C_6-C_1)$_2$ units.[17] Examples of such polyphenolic compounds are the chicoric acids, in which two caffeoyl units acylate the two alcohol functions of tartaric acid,[18a] the dihydroxyphenylethyl glycosides that also bear caffeoyl units, such as verbascoside (*syn.* acteoside),[18b] and the so-called hamamelitannin, which is composed of two galloyl units installed on the rare sugar hamamelose and found in significant quantities in the bark of the witch hazel shrub, *Hamamelis virginiana L.* (Figure 5).[18c]

Through hydration, esterification, and phenolic oxidative coupling reactions, caffeic acid alone also gives rise to oligomeric structures, such as the dimeric rosmarinic acid, up to tetramers, such as rabdosiin and lithospermic acid B (*syn.* salvianolic acid B), which mainly occurs in *Lamiaceae* (formerly known as *Labiateae*) plant species.[19] These caffeic acid derivatives have sometimes been referred to as labiataetannins (Figure 6).[14c,16b]

The most productive plant metabolic route—in terms of the number of (poly)phenolic substances it produces—is without question that leading to the flava/flavonoids. These compounds are metabolic hybrids as they are derived from a combination of the shikimate-derived phenylpropanoid ($\rightarrow$ C_6-C_3) and the acetate/malonate-derived "polyketide" ($\rightarrow C_6$)

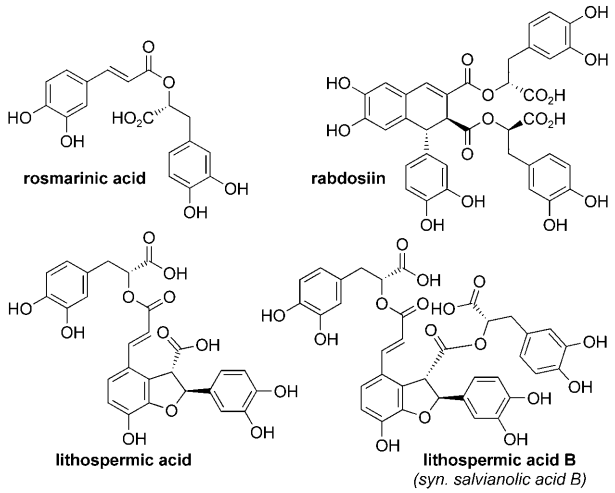


Figure 6. Representative examples of oligomeric labiataetannins derived from caffeic acid.

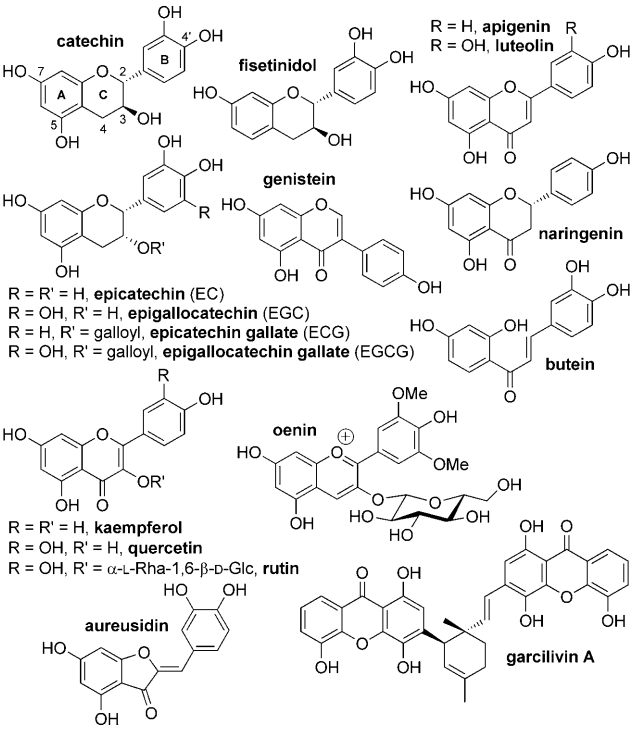


Figure 7. Representative examples of flava/flavonoids.

pathways. Despite this common biosynthetic origin, flavonoids encompass several subclasses of structurally diverse entities. To date, more than 8000 structures have been classified as members of this class of natural products.[20] Most of them are small molecules bearing two mono- to trihydroxyphenyl units with no tanning action, but they can undergo further reactions to give more complex substances with tannin-like properties. They include inter alia flavones such as apigenin and luteolin, flavanones such as naringenin, flavonols such as kaempferol, quercetin and its glycoside rutin, isoflavones such as genistein, anthocyanins such as oenin (malvidin 3-*O*-glucoside),[21] chalcones such as butein, aurones such as aureusidin, xanthones (C_6-C_1-C_6) such as garcilivin A, and last but not least, flavanols such as (epi)-catechin, epigallocatechin, and fisetinidol (Figure 7). These last compounds are the putative precursors of the aforementioned oligo/polymeric condensed tannins (proanthocyanidins) and theatannins (see Figures 1 and 4).

Another substance class with flavanoid-derived oligomeric structures is the intriguing phlobatannins, sometimes referred to as phlobaphenes or tanner's reds. This unique class of ring-isomerized condensed tannins, which has mainly been studied by Ferreira and co-workers,[22] features chromene-type structures such as tetrahydropyrano- or hexahydrodipyranochromenes, respectively, derived from prorobinetinidin-type diflavan-3-ols and profisetinidin-type triflavan-3-ols (Figure 8).[22b]

The hybrid phenylpropanoid/polyketide metabolic pathway also leads to another important class of polyphenolic substances, the polyhydroxystilbenes (C_6-C_2-C_6). The most famous example of which is without a doubt the phytoalexin *trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilbene; Figure 9). In recent years, this compound has been the focus of much scientific attention and media exposure following its biological evaluation as a cancer chemopreventing agent and its occurrence in red wine (see Section 3.3). Polyhydroxystilbenes, which feature a central carbon–carbon double bond conjugated with two phenolic moieties, are particularly prone to undergo oligomerization events presumably through phenolic oxidative coupling reactions. Similar to the hydroxycinnamic acids, esters, and alcohols that are converted into lignan/neolignan dimers $(C_6$-$C_3)_2$ and lignin polymers of the plant cell wall $(C_6$-$C_3)_n$ by related oxidative coupling processes,[23] resveratrol and its natural analogues such as piceatannol (*syn.* astringinin) can react in the same manner and be further (bio)chemically transformed to furnish polyphenolic oligomers, such as ε-viniferin, cassigarol A, pallidol, and the tetrameric apoptosis-inducer vaticanol C (Figure 9).[24]

Would we be pushing the limits of the WBSSH definition too far by proposing that all of the above structure types should be included in the plant polyphenols family? In fact, common literature usage has gone even further by often using the term "polyphenol" to refer to simple plant monophenolic compounds (see Section 2.2). In this context, phenylpropanoid hydroxylated cinnamic acids (C_6-C_3) again have a special status, as their metabolism leads to several additional monophenolics through, for example, decarboxylation, dehydration, hydrogenation, aromatic hydroxylation, oxidative cleav-

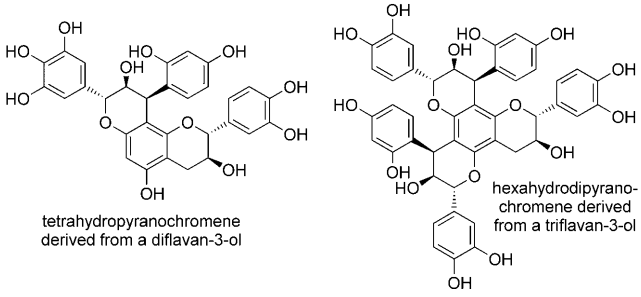


Figure 8. Representative examples of phlobatannins.

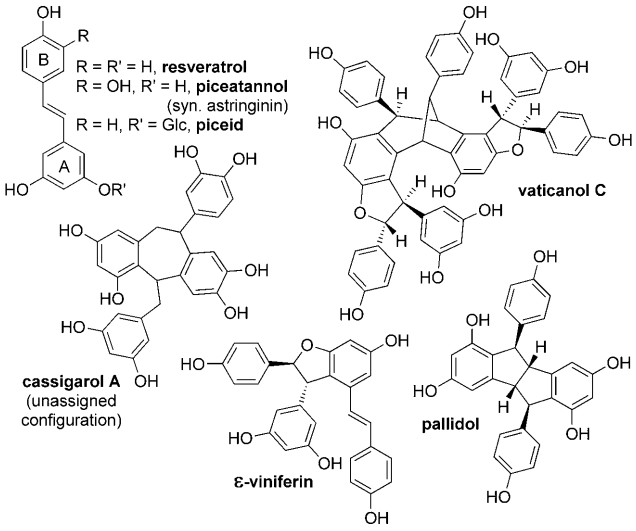


Figure 9. Structures of resveratrol, its glucoside piceid, its catecholic variant piceatannol, and examples of oligostilbenes.

age, and cyclization reactions. Such monophenolics include the aldehydic vanillin (C_6-C_1), the characteristic aroma of fermented vanilla beans, the carboxylic salicylic acid (C_6-C_1), an important agent in plant defence mechanisms, the catecholic hydroxytyrosol (C_6-C_2), a powerful antioxidant extracted from olive oil mill waste waters, eugenol (C_6-C_3), the main aroma of ripe banana and also found in cloves from which it is extracted on an industrial scale, and scopoletin (C_6-C_3), an example of hydroxycoumarins that exert a phyto-

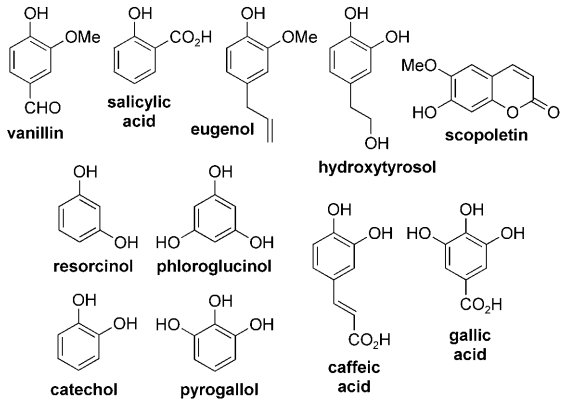


Figure 10. Examples of simple plant-derived "monophenolics".

allexin-like antimicrobial action in plants (Figure 10).[25] These examples and many other monophenolics can play important roles in plants and are often present in plant-derived food and beverages, as well as in traditional herbal medicines. Reports on the study of their chemical, biological, and organoleptic properties are often integrated in polyphenol-related research topics in journals and conferences programs, but that does not mean that they can be referred to as "polyphenols" (see Section 2.2).

2.2. A Comprehensive Definition of Plant Polyphenols

The above assortment of structure types is admittedly far from providing a clear picture of the family of plant polyphenols. Of course, the presence of more than one hydroxy group on a benzene ring or other arene ring does not make them polyphenolic. Catechol, resorcinol, pyrogallol, and phloroglucinol—all di- and trihydroxylated benzene derivatives—are still defined as "phenols" according to the IUPAC official nomenclature rules of chemical compounds.[26] Many such plant-derived monophenolics (see Figure 10) are often quoted as "polyphenols", not only in cosmetic, parapharmaceutic, or nutraceutic commercial advertisements, but also in the scientific literature, which has succumbed to today's fashionable use of the term. The olive-derived antioxidant catecholic hydroxytyrosol (3,4-dihydroxyphenylethanol; see Figure 10) is one flagrant example suffering from such an abuse. The meaning of the chemical term "phenol" includes both the arene ring and its hydroxy substituent(s). Hence, even if we agree to include polyphenolic compounds with no tanning action in a definition, the term "polyphenol" should be restricted in a strict chemical sense to structures bearing at least two phenolic moieties, irrespective of the number of hydroxy groups they each bear. However, as judiciously pointed out earlier by Jeffrey B. Harborne,[27] such a purely chemically based definition of (poly)phenols needs additional restrictions, since many natural products of various biosynthetic origins contain more than one phenolic unit. This is, for example, the case for some terpenoids such as gossypol derived from the cotton plant[28] and many tyrosine-derived alkaloids such as norreticuline[29] (Figure 11). The existence of such alkaloids still gives us

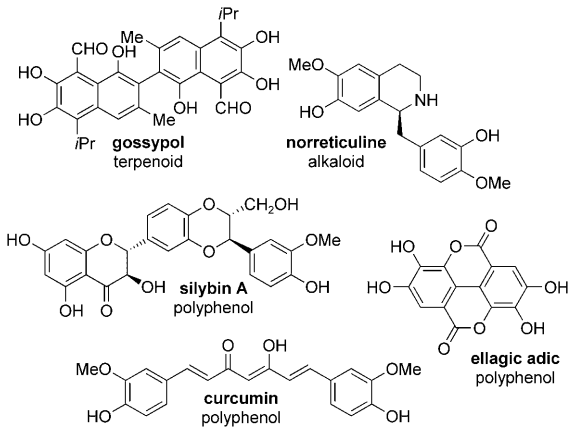


Figure 11. Plant polyphenolic: To be or not to be!

another problem when attempting to define plant polyphenols in an as simple and yet comprehensive manner as possible, since the tyrosine amino acid from which they are derived is itself a (primary) metabolite of the phenylpropanoid pathway. With these considerations in mind, here is our proposal of a revisited definition of "true" plant polyphenols:

The term "polyphenol" should be used to define plant secondary metabolites derived exclusively from the shikimate-derived phenylpropanoid and/or the polyketide pathway(s), featuring more than one phenolic ring and being devoid of any nitrogen-based functional group in their most basic structural expression.

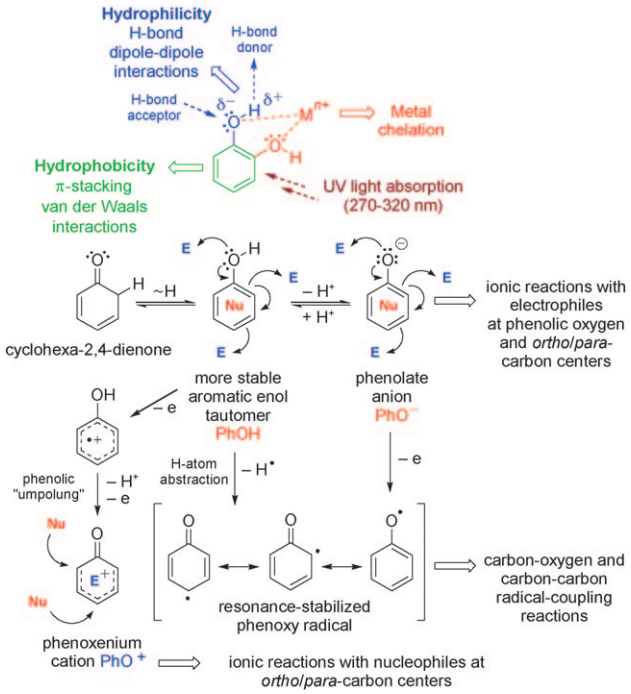
This definition leaves out all monophenolic structures, which include di- and trihydroxyphenyl variants (see Figure 10), as well as all of their naturally occurring derivatives such as methyl phenyl ethers and *O*-phenyl glycosides. Of course, investigations on these compounds, which can be either biogenetic precursors or further metabolites of polyphenols, definitely have their place in polyphenol-related research, but qualifying them as "polyphenols" is pushing it too far. However, all of the structure types mentioned in Section 2.1, including monomeric flava/flavonoids and hydroxystilbenes such as resveratrol and even its glucoside piceid (see Figures 1–9), are "true" polyphenols according to our proposed definition. All of the lignan/neolignan dimers displaying two free phenolic moieties and lignin polymers also fit this definition. Among other plant-derived phenolic compounds that have been the subject of intensive investigations on account of their remarkable biological activities, the ellagitannin metabolite ellagic acid (see Section 3.3), which is naturally present in many red fruits and berries, the phenylpropanoid-derived pigment curcumin, isolated from *Curcuma* spp. such as turmeric (*Curcuma longa*), and the flavonolignan silybin A,[30] isolated from *Silybum marianum* seeds, are also "true" polyphenols (Figure 11).

3. Why Bother with Plant Polyphenols?

There are numerous reasons to investigate plant polyphenols. From their most basic structural expressions to their elaboration into further chemically transformed and complex oligo/polymeric assemblies, plant polyphenols exhibit a remarkably diverse range of bio-physicochemical properties that makes them rather unique and intriguing natural products. The first question that comes to mind is why did plants choose to rely so heavily on the production of metabolites with multiple phenolic moieties. The answer to this question is still a subject of debate and speculation, and possibly differs for the different types of polyphenols.[31] Generally speaking, plant polyphenols, as defined above, have been implicated in diverse functional roles, including plant resistance against microbial pathogens and animal herbivores such as insects (antibiotic and antifeeding actions), protection against solar radiation (screens against DNA-damaging UV-B light), which probably was a determining factor in early terrestrial plant evolution, as well as reproduction, nutrition, and growth, notably through interactions with other organisms above and below ground (insects, symbiotic fungi, and bacteria).[31] Over the course of long-term evolution, as well as compulsory quick seasonal adjustments, plants have learnt to cope with changing environmental conditions and pressures by relying on the formidable chemical arsenal available to them through their remarkably dynamic secondary metabolisms, endless sources of structural

Courtesy of
Prof. Vincenzo Lattanzio

diversity, and variation.[31] Of course, among the main groups of secondary metabolites, others such as alkaloids and terpenoids have also demonstrated their value in protecting plants during their evolution, while contributing by chemical means to maintain a fair ecological balance between plants and other living organisms, many of which feeding on them, including humans. However, plant phenolics arguably deserve a special mention when one considers that the wide-ranging benefits they offer to plants and hence to other living organisms are essentially all a result of their inherent physicochemical properties bundled within the phenol functional group (Scheme 1).



Scheme 1. Basic physicochemical properties and reactivities of the phenol functional group. E = Electrophile, Nu = Nucleophile.

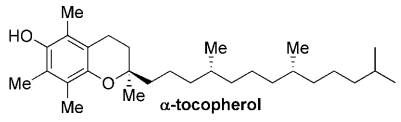
In its most elementary structural form, namely a phenyl ring bearing a hydroxy group (PhOH), a phenol function constitutes an amphiphilic moiety that combines the hydrophobic character of its planar aromatic nucleus with the hydrophilic character of its polar hydroxy substituent, which

can act either as a hydrogen-bond donor or as an acceptor (Scheme 1). Hydrophobic π-stacking (van der Waals) interactions and the formation of hydrogen bonds are seemingly dichotomic, yet are often complementary effects that plant phenolics can use to interact physically with other biomolecules, among which proteins are often first in line (see Section 3.3).[32]

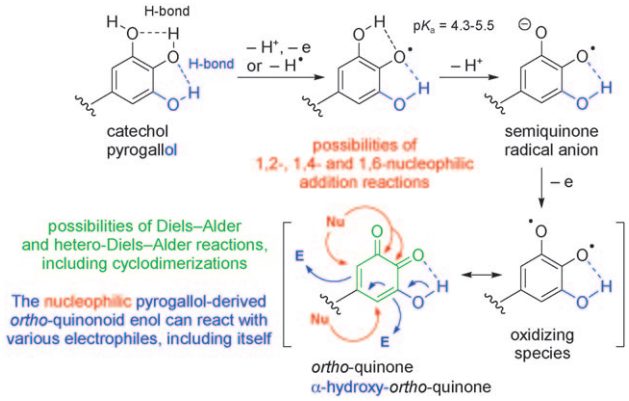
The presence of at least two adjacent hydroxy groups on a phenyl ring open the door to metal chelation,[33] which has also been shown to be an important asset of plant phenolics in their contribution to, for example, plant pigmentation,[21,31b] as well as cationic nutrient (for example, Ca, Mg, Mn, Fe, Cu) cycling through plant-litter-soil interactions.[31b,f,34] Moreover, compared to the secondary ($\pi \rightarrow \pi^*$) absorption maximum of benzene in water at 254 nm, that of phenol is red-shifted to 270 nm. The presence of an additional hydroxy group and/or that of a *para*-positioned electron-withdrawing group such as a carbonyl or a propenoyl ester group, which are often featured in plant (poly)phenolics, further shift the absorption maxima within the UV-B light range (280–320 nm); hence, the phenolic metabolites provide protection against DNA-damaging solar radiation.[31b,c,e]

The adjunction of a single hydroxy group on a benzene (phenyl) ring also has drastic consequences on the chemical properties of this otherwise quasi-inert aromatic system. Phenols can be viewed as stabilized enol tautomers with a soft nucleophilic character, which can be transformed into harder nucleophiles by deprotonation into phenolate anions (PhO^-) as a result of the moderate yet exploitable acidity of the phenolic O–H bond ($pK_a \approx 8$–12) in biological systems. Hence, plant phenolics can be chemically transformed by acting as either carbon- or oxygen-based nucleophiles in various ionic reactions (Scheme 1).

Phenols and phenolate anions are also sensitive to oxidation processes. The relatively weak bond dissociation energy (BDE) of the phenolic O–H bond (87–90 kcal mol^{-1} in the gas phase, up to 95 kcal mol^{-1} in polar aprotic solvents)[35] enables the production of phenoxy radicals ($PhO^{\bullet}$) by hydrogen abstraction. The presence of alkyl and/or alkoxy groups at the *ortho* and/or *para* positions drastically lowers the BDE of the O–H bond, such as for the vitamin E component, α-tocopherol (BDE 77–79 kcal mol^{-1}), the reference standard



antioxidant.[36] Furthermore, phenolate anions can readily be oxidized in a one-electron process to generate delocalization-stabilized radicals, which are often claimed to be key intermediates in the (bio)conversion of simple plant (poly)-phenolics into more complex (oligo/polymeric) polyphenols through carbon–oxygen and carbon–carbon bond-forming radical-coupling events, notably leading to diaryl ether and biaryl constructs. The ability of phenols to homolytically release a hydrogen atom is also one of the fundamental processes that underlies the acclaimed health-benefiting antioxidant properties of many plant-sourced foods naturally rich in polyphenols (see Section 3.1). Dehydrogenative one-electron oxidation processes of catechol- and pyrogallol-type phenols can lead to the formation of *ortho*-quinones and α-hydroxy-*ortho*-quinones, which can behave as electrophilic and/or nucleophilic entities, as well as (hetero)dienes and/or dienophiles in Diels–Alder-type cycloaddition reactions (Scheme 2).



Scheme 2. Oxidative dehydrogenation of catechol- and pyrogallol-type phenols into reactive quinonoid species.

These reactive species have been proposed as conceivable intermediates in the structural elaboration of complex polyphenols in plants (for example, theatannins, oligomeric and complex ellagitannins, as well as dehydroellagitannins such as geraniin; see Figure 4 and Scheme 12) through ionic and/or pericyclic reactions.[15,37] They can also react as electrophiles in the covalent modification of nucleophilic biomolecules such as proteins.[37b,38] In fact, the fate of such potentially toxic quinonoid compounds in biological systems is often overlooked, which is surprising when one considers that these highly reactive, and oxidizing, species can result from the "protective" antioxidant action of their phenolic parents (see Section 3.1). Moreover, under neutral or slightly acidic oxidation conditions, which are typically encountered in biological systems, phenols can be converted into phenoxenium cations (PhO^+) by a sequential two-electron dehydrogenative oxidation process (Scheme 1). These delocalization-stabilized cationic intermediates are potent carbon-based electrophiles.[39]

Must we say more here as to why plants selected the phenol functional group as a special means to equip and elaborate so many secondary metabolites so seemingly useful for their development and survival? It should then not come as a surprise to realize that it is through polyphenolic assemblies that plants manage to best take advantage of the wide range of physicochemical properties exhibited by the phenol functional group, which makes plant polyphenols such remarkably versatile metabolites. It should also come as no surprise that plant polyphenols have long been regarded as a pool of bioactive natural products with potential benefits for human health. Plant extracts, herbs, and spices rich in polyphenolic compounds have been used for thousands of years in oriental traditional medicines. The literature abounds

with reports, mostly published by research scientists from Asian countries in which herbal remedies are still commonly used today, on the identification of polyphenols as active principles of these alternative medications.[13b,16b,40] The regular intake of fruits and vegetables ("five servings per day!")[41] is today highly recommended in the American and European diet, mainly because the polyphenols they contain are thought to play important roles in long-term health protection, notably by reducing the risk of chronic and degenerative diseases.[31d,42] This current, and still increasing, recognition of the benefits brought by plant polyphenols to human health has sparked a new appraisal of diverse plant-derived foods and beverages such as tea, red wine, coffee, cider, chocolate, as well as many other food commodities derived from fruits and berries.

A tremendous increase in the number of scientific publications on "polyphenols" has appeared over the course of the last 20 years (Figure 12). Such reports include numerous epidemiological studies that have confirmed the potential value of these natural products for the prevention of age-related diseases. These studies show that polyphenols act as scavengers of free radicals and reactive oxygen species (ROS, see Section 3.1), which are overproduced under oxidative stress conditions and unable to be subdued by the regular action of endogenous cellular antioxidants such as glutathione (GSH), glutathione peroxidase, or superoxide dismutase, or by dietary antioxidant vitamins (for example, vitamins E and C, carotenoids).

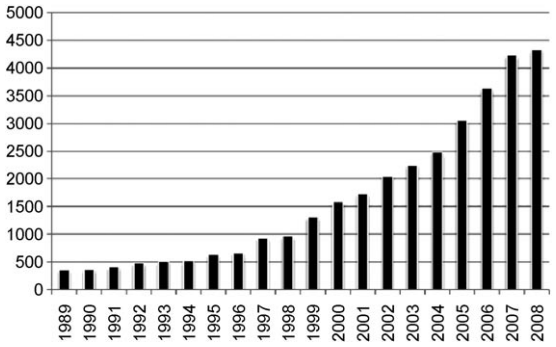


Figure 12. Evolution of the number of publications related to "polyphenols" from 1989 to 2008 (Source: SciFinder Scholar).

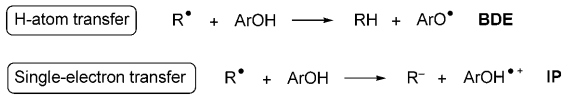
It did not take long for the cosmetic industry to exploit polyphenols extracted from various plant parts, including diverse fruits, herbs, nuts, grape seeds, and tree barks, in their development of new lines of products that aimed to better protect the skin from damages caused by solar radiation and aging. The parapharmaceutic industry has also significantly increased its activities in American and European countries in recent years by proposing new products based on polyphenol-containing plant extracts for various health-preserving purposes; this is an interesting commercial development in which one could perhaps perceive a modern interpretation of traditional medicinal approaches. One famous early example of such parapharmaceutic products is Pycnogenol, a mixture of flavanols, proanthocyanidin oligomers thereof, and phenolic acids extracted from the bark of the pine tree, *Pinus maritima*.[43] The food industry did not stand still and initiated the development of functional foods or "nutraceutics" based on the use of selected natural polyphenolic molecules as additives.[44] The pharmaceutical industry, however, has remained reticent to share the same infatuation for plant polyphenols as possible leads for drug development.[45] One exception is the use of mixtures of proanthocyanidin oligomers extracted from pine tree bark or grape seeds which several decades ago received approval as vasculoprotecting and venotonic drugs (e.g., Flavay, Flavan, Resivit, Endotelon). The reasons for this disapproval of polyphenols by the pharmaceutical industry are somewhat unclear, but medicinal chemists might still be influenced by earlier considerations of plant "tanning" polyphenols as structurally rather undefined oligomeric entities that are only capable of forming precipitable complexes with proteins in nonspecific manners. These considerations might indeed be justified for some plant polyphenols, such as depsidic gallotannins and inextricable mixtures thereof or higher oligomeric proanthocyanidins, but others display structural features that should make them better suited for interacting with proteins, including enzymes, in more specific ways (see Section 3.3). Unfortunately, standard industrial extraction protocols of plant secondary metabolites usually involve a step to ensure the complete removal of all polyphenolic compounds, with many of them being soluble in aqueous phases, to avoid "false-positive" results when screening against a given biomolecular target.[44] Some academic scientists involved in polyphenol research, including ourselves, are of the opinion that it would be worth taking a closer look at these discarded aqueous phases, as they may contain, if not polyphenolic "magic bullets", at least interesting leads for drug development or valuable molecules for probing biological systems.[45,46] Fortunately, the situation is slowly changing, as can be inferred from the increasing number of academic reports from non-"polyphenolists" who demonstrate the value of the unique structural features and biological activities of select members of different subclasses of polyphenolic natural products (see Sections 3.2 and 3.3).

3.1. Polyphenols: Antioxidation or Prooxidation

The most talked about characteristic of polyphenols, and plant phenolics in general, is without doubt their acclaimed capability to scavenge reactive oxygen species (ROS), which include radical and nonradical oxygen species such as $O_2^{-\bullet}$, $HO^\bullet$, $NO^\bullet$, H_2O_2, $^1O_2$, HOCl, as well as oxidatively generated free radicals $RO^\bullet$ and $ROO^\bullet$ such as those derived from biomolecules such as low-density lipoproteins (LDLs),[47] proteins, and oligonucleic acids (DNA and RNA).[48] All these species can have deleterious effects on human health.[31e,42e,49] This so-called antioxidation ability is frequently cited to be the key property underlying the prevention and/or reduction of oxidative stress-related chronic diseases and age-related disorders such as cardiovascular diseases (for example, atherosclerosis), carcinogenesis, neurodegeneration (for example, Alzheimer's disease), as well as skin deterioration, by dietary plant (poly)phenolics and other

plant polyphenol-containing commodities. In view of the overwhelming emphasis that has been rightly or wrongly placed on plant polyphenols as "super" antioxidants, we will briefly describe the fundamental aspects of the chemistry behind it and highlight results from some of the most pertinent investigations made on this topic. Plant (poly)phenolic compounds can also act as antioxidants by chelating metal ions such as iron(II)/copper(I) and iron(III)/copper(II) ions that are involved in the conversion of $O_2^{-\bullet}$ and H_2O_2 into highly aggressive $HO^\bullet$ through Haber-Weiss/Fenton-type reactions.[33,50] They can also block the action of some enzymes responsible for the generation of $O_2^{-\bullet}$, such as xanthine oxidase and protein kinase C.[50b] However, it is through the direct quenching of radical ROS and/or free radicals in general that (poly)phenols (ArOH) appear to best exhibit their protective role. A synergistic antioxidant action through the regeneration of other potent antioxidants such as α-tocopherol (α-TOH; α-$TO^\bullet$ + ArOH → α-TOH + $ArO^\bullet$) is another conceivable option that has also been examined.[50b,51]

Two main antioxidation mechanisms have been proposed.[52] The first is based on the aforementioned capacity of the phenol functional group to donate a hydrogen atom to a free radical $R^\bullet$, such as peroxy radicals $LOO^\bullet$ generated during lipid (LH) autoxidation (peroxidation; LH→$L^\bullet$, then $L^\bullet$ + $^3O_2$→$LOO^\bullet$). In this case, the (poly)phenols act as chain-breaking antioxidants. Through this so-called hydrogen-atom transfer (HAT) mechanism, the phenolic antioxidant (ArOH) itself becomes a free radical ($ArO^\bullet$; Scheme 3). The efficiency



Scheme 3. Hydrogen-atom transfer (HAT) and single-electron transfer (SET) are the main mechanisms through which plant (poly)phenols express their radical-scavenging-based antioxidant action. The dissociation energy (BDE) and the ionization potential (IP) of the phenol are the two basic physicochemical parameters that can be used to determine the potential efficacy of each process, respectively.

of the antioxidant action essentially relies on the rapidity of the H-atom transfer to $LOO^\bullet$ (ArOH + $LOO^\bullet$→$ArO^\bullet$ + LOOH) and on the stability of the resulting phenoxy radical $ArO^\bullet$, which should neither react back with LOOH nor react with the substrate LH, hence terminating the propagating radical chain reaction ($LOO^\bullet$ + LH → LOOH + $L^\bullet$). The ease of formation and stability of $ArO^\bullet$ is strongly dependent upon the structural features of the ArOH parent compound. The most important determining factors are the presence, number, and relative position of additional phenolic hydroxy groups, their implication in the formation of intramolecular hydrogen bonds,[36a] and the conformationally dependent possibility of allowing electronic delocalization throughout the largest part of the molecule. All of these factors affect the BDE of the phenolic O–H bond: the weaker the O–H bond, the easier the H-atom transfer will be.

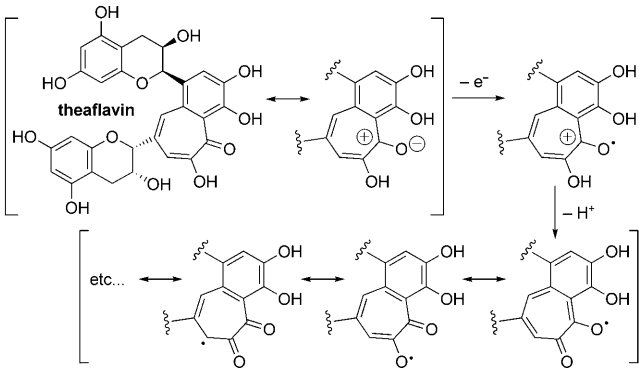
The second mechanism is the single-electron transfer (SET) from ArOH to a free radical $R^\bullet$ with formation of a stable radical cation $ArOH^{\bullet+}$ (Scheme 3). The ionization potential (IP) of ArOH is thus another important physicochemical parameter for assessing the antioxidant efficacy of plant (poly)phenols: the lower the IP, the easier the one-electron transfer is.

In continuation of the outstanding computational work accomplished by Wright et al. that aimed to predict the activity of phenolic antioxidant,[52] Russo and co-workers recently also relied on density functional theory (DFT) calculations of BDEs and IPs, computed in the gas phase, in water, and in benzene, to evaluate the antioxidant activity of a series of representative plant (poly)phenols.[53] Electron-releasing substituents at the *ortho* and/or *para* positions favor H-atom transfer to free radicals by lowering the BDE of the phenolic O–H bond, and stabilize the resulting phenoxy radical by either compensating its electronic vacancy by resonance effects or by hyperconjugation effects, such as in the case of *ortho*-alkyl substituents.[53] Electron-withdrawing substituents at these key positions can also stabilize phenoxy radicals as a result of the delocalization of their unpaired electron through extended conjugation (such as for caffeic acid and its esters). In the case of appropriately positionned combinations of both releasing and withdrawing substituents (such as for gallic acid and its esters), the phenoxy radicals can be stabilized by resonance-driven push-pull effects.[53a] Furthermore, catecholic and pyrogallolic species, such as the plant phenols hydroxytyrosol, caffeic acid, gallic acid (see Figure 10), and the polyphenol epicatechin (see Figure 7), act particularly well as H-atom donors, mainly because of the extra stability confered to the resulting phenoxy radical by hydrogen-bonding interaction(s) with the adjacent hydroxy group(s) (see Scheme 2).[53a] The contribution of such intramolecular hydrogen bonds to the stabilization of phenoxy radicals from catechols and pyrogallols was computed (DFT) in the gas phase to be 8 and 12 kcal mol^{-1}, respectively,[52] and evaluated experimentally (EPR equilibration) to be 4.4 and 7.5 kcal mol^{-1}, respectively.[54] On the basis of the experimentally determined additive contributions of *ortho*-hydroxy and *para*-alkyl groups, the BDEs of the O–H bonds of the polyphenolic epicatechin and epigallocatechin (EC and EGC, see Figure 7) were calculated to be 81.2 and 77.9 kcal mol^{-1}, respectively, in benzene. These values are very close to the experimental value of the reference chain-breaking antioxidant α-tocopherol.[36b,c] Plant polyphenols lacking the possibility of radical-stabilizing intramolecular hydrogen-bond interactions, but exhibiting instead an extended electronic delocalization enhanced by resonance effects and structural planarity, such as for the flavonol kaempferol and the trihydroxystilbene resveratrol (see Figures 7 and 9), were calculated to have lower IP values. Such polyphenols were thus considered to be antioxidants more prone to act by transferring an electron to free radicals.[53a] In recent related computational studies carried out by Zhang et al.,[55a] plant polyphenolic flavonoids featuring a catechol moiety were also characterized by relatively low BDEs for the O–H bond: the value for the catecholic B ring of the flavanol catechin was, for example, lower than that of the corresponding ring in the flavone luteolin (see Figure 7).[55a] It was then argued that the presence of a conjugated electron-withdrawing group *para* to

a phenolic O–H bond—such as the conjugated enone unit in the C ring of luteolin and other flavones as well as flavonols—is not beneficial for reducing its BDE, it would in fact have an opposite effect.[55] However, as stated above, an electron-withdrawing *para* substituent can be beneficial to the stabilization, by electronic delocalization, of the phenoxy radical, if/when formed. One could then argue that highly conjugated systems such as those in flavones and flavonols with appropriate IPs might then be better at stabilizing phenoxy radical cations generated by a SET process, in accordance with the conclusions of Russo and co-workers.[53a]

What can be deduced from the large amount of literature data available today on (poly)phenolic antioxidants at the fundamental level? Firstly, experimental BDE values, most often determined by EPR equilibrium spectroscopy and photoacoustic calorimetry techniques, can be reproduced fairly well by DFT calculations. Secondly, the contribution of a given substituent to the modulation of the BDE of the O–H bond is approximately constant, so that a group additivity rule can be applied to calculate BDE values of variously substituted (poly)phenols.[52,53] Such predictions of BDEs of phenolic O–H bonds on the basis of the additive contributions of different substituents are considered to be quite reliable, useful for the design of novel synthetic antioxidants, and particularly revealing when attempting to rationalize the numerous experimental data available from structure–activity relationship studies on the antioxidative effects of plant polyphenols.[47,50b,56] A divergence between calculated and experimental BDE values thus constitutes a strong indication that a mechanism different from HAT, such as SET, and/or some other kinds of modulating effects (steric demand of phenolic *ortho* substituents, hydrophilicity/lipophilicity of the antioxidant, hydrogen-bonding characteristics of the solvent) are operative.[52,55b,57]

Numerous techniques have been developed to evaluate the antioxidant capacity of plant (poly)phenols, essentially all based on monitoring directly or indirectly the decay of radical species and on determining the rate constants for radical scavenging.[47,50b,56,58] For example, Jovanovic et al., then Bors and Michel, relied on pulse radiolysis to evaluate the reactivity of various polyphenols with $HO^{\bullet}$, $O_2^{-\bullet}$, and $N_3^{\bullet}$.[56c,e] Bors and Michel suggested that flavanols such as (epi)catechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), epigallocatechin gallate (EGCG; see Figure 7), and oligomers thereof (proanthocyanidins; see Figure 1) are better radical scavengers than many monomeric flavones and even flavonols. The reason for this is their (multiple) expression of catecholic and pyrogallolic moieties as privileged radical-scavenging sites. The increasing rates of reactions with the highly reactive $HO^{\bullet}$ species ($t_{1/2} \approx 10^{-9}$ s) nicely correlated with the number of phenolic units bearing adjacent hydroxy groups.[56c] The bispyrogallolic EGCG was the most reactive compound among the monomeric flavanols tested ($k = 7.1 \times 10^9\,\text{M}^{-1}\text{s}^{-1}$). Moreover, the pentapyrogallolic hydrolyzable tannin β-PGG (1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose; see Figure 13, Section 3.3) exhibited a reaction rate one order of magnitude higher than that of EGCG.[56c] Interestingly, the flavanol-derived black tea theaflavin was found to scavenge $O_2^{-\bullet}$ at neutral pH at a rate about one order of magnitude higher than that of EGCG ($k = 10^7$ versus $7.3 \times 10^5\,\text{M}^{-1}\text{s}^{-1}$). This surprisingly high antioxidant potential was attributed to the electron-transfer capability of the theaflavin benzocycloheptenone motif, which gives rise to a highly acidic radical cation species that rapidly deprotonates to afford a neutral radical, strongly stabilized by delocalization of the unpaired electron throughout the entire motif (Scheme 4).[56e]



Scheme 4. Efficient SET from the benzocycloheptenone moiety of the black tea theaflavin leading to a tropilium radical cation. Rapid deprotonation then furnishes a highly resonance-stabilized neutral radical.

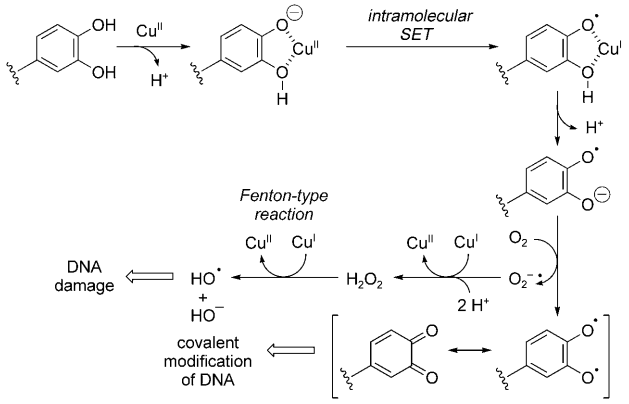
Extensive structure–activity relationship studies have been carried out on large numbers of plant polyphenols by relying on numerous antioxidation activity assays, notably based on the ability of an antioxidant to scavenge the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation ($ABTS^{+\bullet}$) in comparison to that of the water-soluble vitamin E analogue Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) or to scavenge the 1,1-diphenyl-2-picrylhydrazyl radical ($DPPH^{\bullet}$). Determining the ability of an antioxidant to inhibit copper(II)- or 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced LDL peroxidation is another option. All of the assays unveiled more or less the same trends.[47,50b,56]

Among the flavo/flavanoid polyphenols, the presence of a catecholic B ring definitely stands out as the most influential factor in terms of the best antioxidant activity. Flavonols are usually more active than flavones, provided that the 3-hydroxy group on their C ring remains unglycosylated. The corresponding electron-releasing enol unit on the flavonol probably counteracts the detrimental effect of the electron-withdrawing enone unit with which it shares its carbon–carbon double bond. Thus, for example, the potent antioxidant flavonol quercetin is much more active than its 3-*O*-glycoside rutin, and both are more active than kaempherol (see Figure 7). Having only a monohydroxylated B ring, this flavonol is even less active than the catecholic flavone luteolin, which is itself slightly less active than the (epi)catechin flavanols.[56d,g] This ranking of antioxidant activity is perfectly in line with the results of the computational studies highlighted above.[53a,55a] A pyrogallolic B ring and/or a galloyl unit on the 3-hydroxy group of the C ring in flavanols, such as EGC, ECG, EGCG, and/or their oligomerization into proan-

thocyanidin constructs render them at least equipotent to quercetin, if not even more active.[56a,d,g] This trend is in agreement with the aforementioned results and suggestions of Bors and Michel.[56c] Anthocyanidins, as well as their 3-*O*-glycosides, can also be equipotent to quercetin, again as long as their B ring is a catechol or a pyrogallol moiety.[56g] Thus, unsurprisingly, not only the gallotannin β-PGG (see Figure 13, Section 3.3), but also ellagitannins and their oligomers with increasing numbers of galloyl and galloyl-derived bi/teraryl units were found to be highly potent antioxidants, with activities by far surpassing those of most flavonoids.[47e,56d]

However, it must also be recalled that plant polyphenols bearing catechol and/or pyrogallol moieties can, under certain circumstances, exert prooxidant properties, notably by reducing iron(III) or copper(II) ions that they chelate.[33b] Furthermore, as alluded to above, the *ortho*-hydroxyphenoxy radical produced from the oxidation of a catechol/pyrogallol moiety (see Scheme 2) can also react with a second free-radical species, including $^3O_2$, to afford oxidizing *ortho*-quinones and $O_2^{-\bullet}$. The consequence of these prooxidant activities is that catecholic (and pyrogallolic) plant (poly)phenols can, for example, induce DNA breakage in the presence of $^3O_2$ and iron or copper species, most significantly copper(II) ions because of their lower standard reduction potential: $Cu^{2+}/Cu^{+} \rightarrow 0.15$ V versus $Fe^{3+}/Fe^{2+} \rightarrow 0.77$ V.[33b,48a,59]

Thus, catechol and pyrogallol moieties can suffer a dehydrogenative one-electron oxidation and thus reduce copper(II) to copper(I) ions, which are then involved in the reduction of $O_2^{-\bullet}$. The $O_2^{-\bullet}$ ion is itself generated by the reduction of $^3O_2$ by *ortho*-hydroxyphenoxy radicals (from catechol/pyrogallol) or, and most probably in biological systems, by their corresponding semiquinone radical anions, since the *ortho*-hydroxyphenoxy radical parents are remarkably acidic ($pK_a = 4.3$–5.5).[56f] More copper(I) ions can then convert H_2O_2, which is produced from the copper(I)-mediated reduction of $O_2^{-\bullet}$, into DNA-damaging $HO^{\bullet}$ through a Fenton-type reaction (Scheme 5). Moreover, the electrophilic *ortho*-quinones thus generated from the one-electron oxidation of semiquinone radical anions can then also induce covalent DNA damage, as well as protein and peptide covalent modifications (see Schemes 2 and 5).[37b,38,60]



Scheme 5. Proposed prooxidation mechanism for copper(II)-mediated DNA damage by catecholic (or pyrogallolic) plant (poly)phenols.

So here comes the dilemma! Are plant polyphenols protective antioxidants or toxic prooxidants? Are they free-radical scavengers or producers? Is their metal-chelating action beneficial for antioxidative protection or does it promote the reduction of certain metal ions into ROS-generating species? As often in science, the simplest answer to all of these related questions hides a great amount of complexity: "it depends!" For sure, the appraisal of plant polyphenols as antioxidant agents must be considered with a great deal of caution, especially in view of the growing number of industrial applications in processed commodities, as their activity depends on many factors such as their particular structural and chemical reactivity features, redox potential versus those of the species with which they interact, the BDE and IP of the phenol unit, concentration, solubility, metabolism and, more generally, bioavailability,[42a,d,61] as well as the bio-physicochemical characteristics of the medium in which they can exert their action (for example, matrix and cell type, chemical composition, redox state and cycling, pH value, metallic ion type and concentration). In brief, one must always keep in mind that plant polyphenols are first and foremost redox-active compounds and can thus indeed either act as antioxidant or as prooxidant entities. With such a consideration in mind, some researchers have started to revisit the possible modes of action of plant (poly)phenols, notably in the context of their chemopreventive role against carcinogenesis.

For example, Liu, Zhou, and co-workers have recently studied the above prooxidation scenario in detail for the case of caffeic acid and resveratrol derivatives.[62] Copper(II) ion chelating phenolate anions derived from catecholic species most strongly induced DNA breakage and exhibit antiproliferative cytotoxicity against human promyelocytic leukemia (HL-60) cells in a dose-dependent manner. It would thus appear that, in normal cells, select plant (poly)phenols at relatively low concentrations could express a cancer chemopreventing effect by virtue of their antioxidative HAT-based ROS-scavenging properties. In cancer cells, however, which are generally characterized by a higher oxidative stress level,[63] plant (poly)phenols at higher concentrations could instead act as prooxidants through a sequential proton-loss SET-based reduction of copper(II) ions (Scheme 5), by further increasing ROS production and hence promoting cytotoxic DNA breakage. This prooxidation-based postulate provides a firm ground for future investigations on the development of polyphenol-inspired selective anticancer agents.

3.2. Polyphenols and The "Wine Factor"

One of the factors that has undeniably and significantly boosted research interest in plant polyphenols is the seminal epidemiological study by Serge Renaud on the so-called "French paradox", which unveiled a lower incidence of coronary heart diseases in France as a consequence of the regular drinking of wine, and this, despite a high dietary intake of fat.[64] Wine, and red wine in particular, is extremely rich in polyphenols derived from grapes. These polyphenols

include flavanols and their proanthocyanidin oligomers, anthocyanins, hydroxylated stilbenes such as resveratrol, flavonols such as kaempferol and quercetin, and their pyrogallolic B-ring variant myricetin, as well as ellagitannins and ellagic acid derived from oak as a result of the aging of wine in oak barrels.[66] The total amount of polyphenols in red wines has been estimated to range from near 2000 to about 6000 mg L^{-1}, with the greatest contribution coming from the (oligo)flavanol [1000–5000 mg L^{-1}, including catechin at 100–200 mg L^{-1} and epicatechin at about 80 mg L^{-1}] and anthocyanin (100–1500 mg L^{-1}) fractions.[61a,66] For some obscure reasons it is one of the minor polyphenolic components of wine, *trans*-resveratrol (ca. 0.1–8 mg L^{-1}, and ca. 1–50 mg L^{-1} for its glucoside *trans*-piceid; see Figure 9),[67] that has received much research attention.[68] It was, for example, found that resveratrol could inhibit LDL peroxidation and platelet aggregation, which is in line with Renaud's postulate on the impact of red wine drinking on the decrease of coronary heart disease.[69] However, contradictory results were obtained on the capacity of resveratrol to act as an antioxidant in comparison to other polyphenols present in wine.[69a] Recent studies show that resveratrol is indeed neither a potent antioxidant nor even capable of efficiently regenerating α-tocopherol (the BDE of its 4′-OH bond is about 3 kcal mol^{-1} higher than that of α-TOH).[52,70] Only resveratrol derivatives bearing a catecholic B ring showed a remarkable antioxidant efficacy.[70a] One can then certainly wonder why resveratrol, and not its naturally occurring catecholic variant piceatannol (see Figure 9), received most of the attention as the presumed main contributor to the total antioxidant power of red wine, not to mention all of the other and often much better polyphenolic antioxidants present in red wine.[64c,69c,71]

A second major thrust for the scientific popularity of resveratrol came from a report by Pezzuto and co-workers in *Science* on the chemopreventive action of this simple polyphenol.[72] In a dose-dependent manner, resveratrol was again found to express antioxidant effects, to act as an antimutagen, to induce phase II enzymes, to mediate anti-inflammatory effects, to inhibit the cyclooxygenase and hydroperoxidase functions of COX-1, and to induce the differentiation of HL-60 cells into a nonproliferative phenotype. Resveratrol was thus shown to be capable of acting on cellular events associated with tumor initiation, promotion, and progression. Nearly 2000 publications on resveratrol ensued over the past few years, some confirming, others disproving, many expanding, but all debating the results of Pezzuto's seminal study.[73] It was found that resveratrol is capable of acting in multiple ways through multiple pathways involved in the regulation of the cell cycle and the induction of apoptosis by modulating directly or indirectly in a dose- and cell-status-dependent manner either prosurvival or proapoptotic factors such as hormone-regulated receptor signaling systems (for example, estrogen receptors) and the expression and/or activity of numerous functional proteins such as the tumor-suppressor p53 and retinoblastoma (pRb) proteins, MAP kinases, cyclins and cyclin-dependent kinases, tyrosine kinases (for example, Src), other protein kinases (for example, B/Akt, C, D), DNA polymerase (in vitro), carcinogenic phase I (for example, cytochrome P450 monooxygenases, CYPs) and phase II enzymes, proinflammatory cyclooxygenases (COXs), lipoxygenases (LOXs) and induced nitric oxide synthase (iNOS), both anti- and proapoptotic Bcl2 proteins, proliferative transcriptional factors (for example, NF-kB, AP1, Egr1), and co-transcriptional factors such as the acetylase p300, known to activate the proliferative NF-kB, as well as the apoptotic p53, and the deacetylase sirtuin 1 (SIRT1), presumed to exert the exact opposite effects.[73d] Recently, resveratrol was also found to exert an antimetastatic effect by blocking tumor cell adhesion to endothelial cells through the inhibition of the expression of ICAM-1, a glycoprotein cell-surface receptor involved in cell–cell interaction processes.[74] The apparent dichotomy that emerges from the reported data on resveratrol does not help the establishment of a clear picture of its effects on human health. However, it does at least unveil its conceivable and remarkable capacity to act as a promoter of either cell death or survival by interacting with different target molecules to affect signaling pathways within cells in different ways depending upon their status and related specific molecular settings. If this ability of resveratrol is remarkable, it is likely not unique, as it can be inferred from similar data related to the chemopreventive and/or chemotherapeutic actions of other plant polyphenols, notably those found in tea such as EGCG,[75] or in curry powder such as curcumin (see Figures 7 and 11).[76]

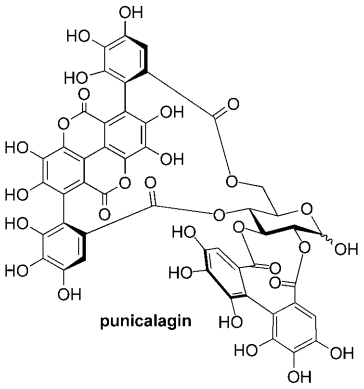
Interestingly, not only resveratrol, but also piceatannol and the flavonol quercetin, all three present in wine, were found by Howitz et al. to activate the aforementioned gene transcriptional regulator SIRT1. SITR1 is a human NAD^+-dependent deacetylase that promotes cell survival by inactivating the p53 protein, hence delaying apoptosis to give cells additional time to repair damage before cell death.[45,77] Resveratrol was the most potent activator and at low doses (0.5 μM) increased the survival of human embryonic kidney (HEK) cells submitted to radiation-induced DNA-damaging conditions. A reverse effect was, however, observed at higher concentrations (50 μM). Most intriguingly, resveratrol was also able to mimic calorie restriction in yeast by activating Sir2 (the yeast homologue of the human SIRT1), hence extending the average cell lifespan by 70%.[45,77] In a recent study by Das and co-workers, the expression of SIRT1 and other related so-called "longevity" proteins were induced in rats fed with both red and white wines.[78]

The SIRT1 enzyme has also been shown to confer significant protection against age-related neurodegeneration, notably by rescuing neurons from Alzheimer's disease.[79] Since resveratrol has also been shown to promote the intracellular degradation of β-amyloid peptides,[80] which play a central role in the pathogenesis of the disease, its capacity to activate SIRT1 also makes it hold promise for developing therapeutic strategies against Alzheimer's disease. However, scrutinization of the original data on the activation of sirtuins by resveratrol at the molecular level has led to much controversy.[81] In fact, it now seems very unlikely that resveratrol is a direct activator of SIRT1,[81b] but it could still be a promising drug candidate or lead for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, as well as for type II diabetes mellitus, by virtue of its ability to

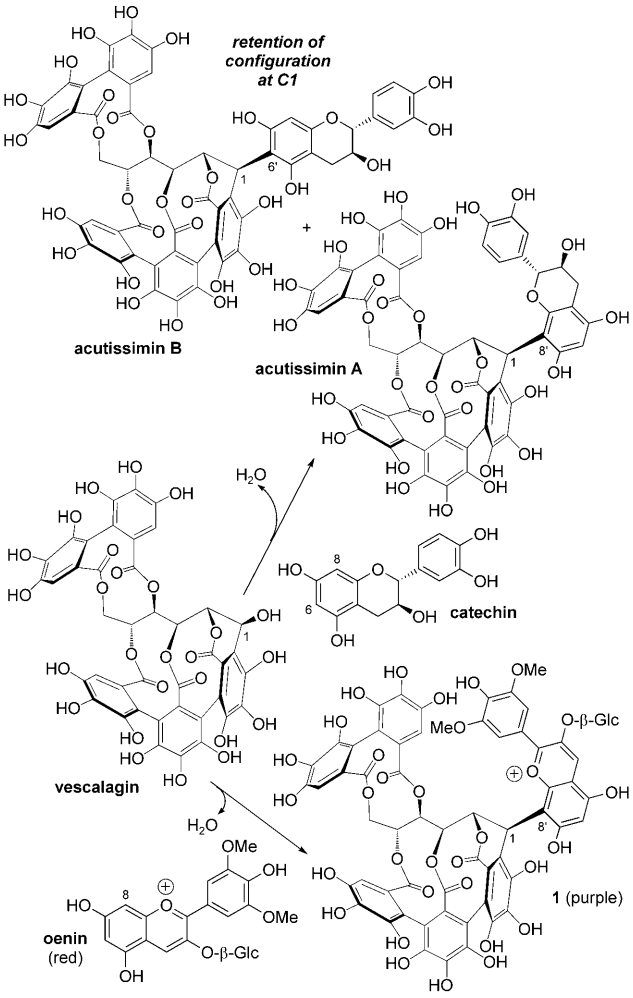
directly inhibit amyloid fibrillogenesis resulting from the misfolding and aggregation of polypeptides such as β-amyloid (βA), α-synuclein (αS), and islet amyloid polypeptide (IAPP; see Section 3.3).[82] We should also mention here that such anti-Alzheimer activity of resveratrol might be in line with the results of several epidemiological studies that indicate that moderate wine intake is associated with a lower incidence of Alzheimer's disease.[83]

However, resveratrol is just one among many other bioactive polyphenols present in wine. One particular subclass of polyphenols that has been somewhat overlooked in this context is composed of members of the ellagitannin family (see Figure 2). The multiple pyrogallol-type galloyl units in these polyphenols make them particularly strong antioxidants,[47e,56d] but it is on their antimicrobial, antiviral, and (host-mediated) antitumor activities that most of the attention was and still is focused.[84] The question of the bioavailability of ellagitannins has recently been the subject of much concern, notably because of their occurrence in fruits and nuts, such as pomegranate, berries, and walnuts, and because of conflicting claims for beneficial versus toxic effects caused by ellagitannins and/or their metabolites.[61f] Although studies on ellagitannin-rich dietary foodstuffs have demonstrated their anticancer action through pro-apoptotic effects and the inhibition of subcellular signaling pathways of inflammation, angiogenesis, and tumor cell proliferation,[85] investigations on bioavailability concluded that ellagitannins are essentially not absorbed in vivo, but hydrolytically release the bislactone ellagic acid (see Figure 11), which is then metabolized by the human gut microflora into so-called urolithins (hydroxylated dibenzopyranones). Ellagic acid and some of its metabolites would in fact be the agents responsible for the anticarcinogenic effects of dietary ellagitannins observed in vivo.[86]

It is, however, important to recognize that the aforementioned bioavailability studies[86] have been performed using only a few ellagitannins, all of which were members of the readily hydrolyzable $^4C_1$-glucopyranosic subclass, such as pedunculagin (see structure in Figure 22) and punicalagin.



The ellagitannins that are present in wine as a result of their extraction from oak wood during wine aging in oak barrels belong to another and putatively more robust subclass of ellagitannins, the *C*-glucosidic variants, exemplified by vescalagin (see Figure 2). These ellagitannins have the unique structural characteristic of featuring an open-chain glucose core linked through a C–C bond to one of their galloyl-derived units.[87] To the best of our knowledge, no specific bioavailability data exist on these compounds, which have also been found to exhibit potent antiviral- and antitumor-related activities.[88] Of particular note is our recent demonstration of the presence in wine of potent *C*-glucosidic flavano-ellagitannic inhibitors of human DNA topoisomerase IIα (in vitro), known as acutissimins (see Scheme 6),



Scheme 6. Hemisynthesis of flavano- and anthocyano-ellagitannins from the oak-derived vescalagin and grape-derived wine flavonoids.

which were first isolated from the bark of the oak species *Quercus acutissima*.[89] Not present in the oak heartwood used to make barrels, these *C*-glucosidic complex ellagitannins are generated during the aging of wine in barrels, as a result of acid-catalyzed chemo- and stereoselective nucleophilic substitution reactions between vescalagin and the grape-derived catechin.[65b–d] Similar reactions with other wine nucleophiles have also been shown to operate in mildly acidic (pH 3–4) hydroalcoholic wine model solutions, notably an intriguing condensation reaction between vescalagin and the red-colored grape-derived pigment oenin that furnishes a novel

purple-coloured anthocyano-ellagitannin hybrid pigment **1** (Scheme 6).[65a,c]

The color is not the only organoleptic property of wine that can get modulated by the presence of *C*-glucosidic

ellagitannins. Interestingly, some of their deoxygenated and dehydrogenated derivatives produced during the toasting of oak barrels have been identified as "taste-active" compounds. Human sensory experiments have revealed that these derivatives impart an astringent mouth-coating sensation.[90] However, the polyphenols that have been subjected to most studies in relation to their influence on wine astringency—that feeling of drying and puckering experienced in the mouth when tasting red wines—are the grape-derived flavanol-based condensed tannins (proanthocyanidins), which are the most abundant polyphenols in wine. That feeling of astringency, also sometimes experienced when drinking oligoflavanol-rich black tea, results from the formation of precipitating complexes with proline-rich salivary proteins, as we shall discuss in the following section.

3.3. Polyphenols and Proteins—Nonspecific Complexation or Drug/Target-like Interaction?

For a long time, the biological activities of plant polyphenols in plants, as well as in humans, have arguably been attributed to their capacity to exert antioxidant actions (as discussed above) and/or to their propensity to form precipitating complexes with proteins in a rather nonspecific manner.[40d,91] Today, there is compelling evidence that strongly suggests that the mechanisms by which plant polyphenols exert their protective actions against cardiovascular and neurodegenerative diseases, as well as cancer and diabetes, are not simply due to their redox properties, but rather to their ability to directly bind to target proteins (or peptides). Such a mode of action would induce the inhibition of key enzymes, the modulation of cell receptors or transcription factors, as well as the perturbation of protein (or peptide) aggregates, which can regulate cell functions related to, for example, growth and proliferation, inflammation, apoptosis, angiogenesis, metastasis, and immune responses, in various ways by affecting signal transduction pathways.[46a,75a,d,92] In addition to the examples mentioned in the previous section, numerous other reports describe the significant inhibition of various enzymes by various polyphenols.[31e,32,46a,61b,75a] Among the most therapeutically relevant enzymes are inflammatory ones such as COXs and LOXs, CYPs, signal transduction kinases (generally inhibited more strongly by simple flavonoids, ellagitannins, and ellagic acid than by gallotannins and condensed tannins[93]), xanthine oxidase, NADH-oxidase, thioredoxin reductase,[94a] adenosine deaminase, matrix metalloproteinases,[94b] telomerase, DNA polymerases,[94c,e] topoisomerases and methyl transferases, ATPase/ATP synthase,[94d] ornithine decarboxylase, as well as urokinase, an enzyme required by human tumors to form metastases and notably inhibited by EGCG (Figure 7).[95]

The current appreciation of the capacity of several plant polyphenols to modulate cellular signaling cascades by binding to specific target proteins has certainly refreshed opinions on polyphenol–protein interactions, and should provide a new impetus for (re)considering polyphenolic compounds in pharmacological drug developments. We emphasize again that the structural diversity of plant polyphenols is huge, and that the manner with which they can interact (specifically or not) with proteins strongly (and mutually) depends on both their physicochemical characteristics and those of their protein partners. In this regard, William V. Zucker's article published in 1983 in *The American Naturalist* on the ecological "raison d'être" of condensed and hydrolyzable tannins in plants is highly recommended.[31k]

Early research interest on polyphenol–protein interactions focused on understanding the mechanistic and fundamentals of molecular recognition of the precipitation of proteins by polyphenols. This is a general process that underpins some forms of chemical defence in plants, modes of action of traditional herbal medicines, astringency, as well as the conversion of animal skins into leather.[40d,91] In his seminal study in 1974, Haslam examined the association of a series of galloylated D-glucoses, including gallotannins, and condensed tannins with the β-glucosidase protein by measuring the remaining enzymatic activity in the supernatant solution.[96] The presence and, to some extent, the number of pyrogallolic (galloyl) and catecholic units were found to be essential for the precipitation of the enzyme, possibly as a result of extensive hydrogen-bond formation with ketoimide groups of β-pleated sheet portions of the enzyme. The gallotannic β-PGG structure (see Figure 13) was identified among the molecules tested as representing the optimum configuration for binding to the enzyme in a ratio of approximately 1 molecule of the enzyme to 20 molecules of the polyphenol.[96] In the following years, the ability of polyphenols to strongly associate with proteins with a high proline content was clearly established[97] and the molecular interactions of polyphenols with proline-rich proteins (PRPs) in saliva were examined in detail, notably in relation to the phenomenon of astringency. NMR spectroscopic analyses of complexes formed between different polyphenols and model peptides mimicking extended polyproline helices of PRPs were performed, and some details of the association between β-PGG and mouse salivary proline-rich peptides were then revealed.[98] A preference for an interaction between the pyrolidine ring of prolyl groups and the aromatic ring of galloyl units (σ-π attraction) was thus discerned, in tandem with the deployment of hydrogen bonds between the carbonyl

group of the peptide residue preceding the proline unit and one of the *meta*-hydroxy groups of the β-PGG galloyl moieties (Figure 13).[98a,c] This selectivity for proline residues

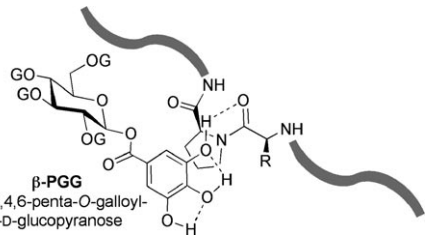


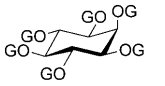
Figure 13. Proposed interaction between a β-PGG galloyl group and a prolyl residue with formation of a hydrogen bond with its preceding amide bond; G = galloyl (3,4,5-trihydroxybenzoyl).[98a,c]

was, however, challenged in the case of the complex formed between Gly-Pro-Gly-Gly and the procyanidin B_3 catechin-(4α→8)-catechin, for which no preferential interaction with the proline residue was observed.[99]

Numerous other studies, using either peptides or full-length proteins and various polyphenolic molecules, have been carried out over the years to provide further insight into the physicochemical basics that govern polyphenol–protein complexation (and precipitation). The aim of these studies was not just understanding the astringent effect of dietary polyphenols, but also how their binding to proteins could affect (not necessarily negatively) their biological activities, including their antioxidant action, and their bioavailability.[32,100] These studies relied on a large panoply of analytical techniques, including again NMR spectroscopy,[101] as well as circular dichroism,[101a,d,102] mass spectrometry,[101d,103] Fourier transform infrared spectroscopy,[104] dynamic light and small angle X-ray scattering,[102,105] transmission electronic microscopy,[102b,105b] calorimetry,[102a,106] equilibrium dialysis,[106c,107] size-exclusion chromatography,[108a] nephelometry,[108b] fluorescent quenching,[108c] and quartz crystal microbalance with dissipation.[108d] Some of the most pertinent, although sometimes apparently conflicting, elements of discussion drawn from these investigations can be summarized as follows:

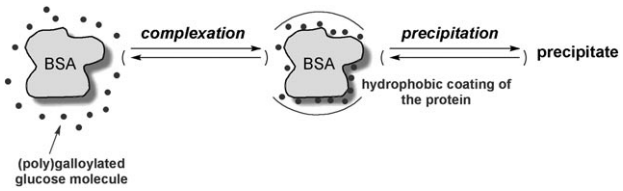
Hydrophobic effects are usually considered to be the predominant cause of association, which is then further stabilized by hydrogen bonding. In the case of PRPs, hydrophobic stacking of phenolic rings against proline rings would constitute the primary associative driving force, followed by the formation of hydrogen bonds between phenolic hydroxy groups and carbonyl groups linked to proline amino groups, hence stitching up the resulting complex (Figure 13).[91a] However, some researchers have suggested that the principal driving forces towards association are instead governed by hydrogen bonding between the carbonyl groups of proline residues and the phenolic hydroxy groups.[97a,101d,109] In any event, large (oligomeric) polyphenols would then be capable of simultaneously binding to several proline sites in a polydentate fashion, perhaps even self-associating once bound to provoke the precipitation of polyphenol–polyphenol–protein complexes.[98a]

The nature and extent of the interactions between polyphenols and proteins strongly depend on the chemical structure and related physical properties of the polyphenol. Galloylation of flavanols such as in ECG and EGCG (see Figure 7) enables complexation with, and even precipitation of, proteins (including PRPs).[102a,106b] These 3-*O*-galloylated flavan-3-ols are among the smallest polyphenols capable of such a performance. Increasing the number of galloyl groups on a D-glucopyranose core would promote an increase in the protein-binding capacity until the optimum β-PGG structure is reached (see Figure 13); further galloylation, as in gallotannins, does not lead to any significant improvement.[96] The position of galloyl groups on the sugar core would slightly influence the binding affinity to proteins, as shown by the standard test-case protein bovine serum albumin (BSA).[110] The stereochemistry of the sugar core can also have a significant impact, as shown in the case of α-PGG, which has a measurably greater affinity for BSA than does the natural β diastereomer.[107] The axial orientation of the O-1 galloyl group in α-PGG was proposed to confer a more open structure to the molecule, hence exposing some galloyl units better for hydrophobic interactions with proteins compared to the more compact all-equatorial pentagalloylated species β-PGG.[107] This molecule would then represent the optimum structure for protein binding only among (known) naturally occurring galloylated glucose derivatives and related gallotannins. Thus, a synthetic analogue of β-PGG, the hexagalloylated *myo*-inositol, was found to have an affinity about six times greater than that of β-PGG for BSA.[107]



The conformational flexibility of polyphenols definitely constitutes an important determining factor of their ability to interact with proteins. Interestingly, although β-PGG (in which all five galloyl groups are free) has the same number of galloyl groups and about the same molecular mass (only six hydrogen atoms more) as the conformationally constrained biaryl/terarylated open-chain D-glucose derivative vescalagin (or its C-1 epimer castalagin; see Figure 2), the extent of its association with BSA is about 30 times greater than that of vescalagin/castalagin.[91a,106c] Similar observations were made using the same polyphenols and collagen,[111] as well as the peptide model bradykinin,[101b] both proline-rich and rather hydrophobic in character. It is also noteworthy that β-PGG has a very limited solubility in water (with an octan-1-ol/water partitioning coefficient K_{ow} of 32), while the *C*-glucosidic ellagitannin vescalagin (and ellagitannins in general) is highly hydrophilic with a K_{ow} value of 0.1.[112] It is from these observations that Haslam proposed that the less hydrophilic the polyphenol, the better is its ability to complex with proteins,[91a] at least with extended random-coil type proteins such as salivary PRPs, collagen (or gelatin), casein, as well as peptides such as bradykinin, or loosely structured globular proteins such as BSA. Kawamoto et al. proposed a follow-up two-stage process for the precipitation of BSA by galloylated glucose derivatives (Scheme 7).[110]

The first stage in this process is a complexation between the protein and those polyphenols bearing a minimum

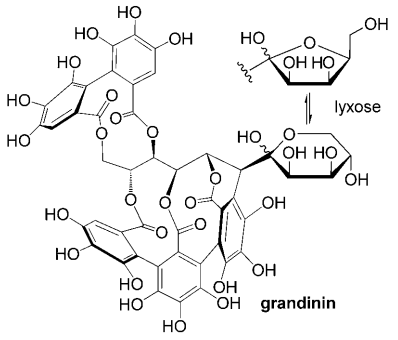


Scheme 7. Two-stage process for the precipitating complexation of BSA by gallotannin-like "hydrophobic" galloylglucopyranoses.[110] For complexation, more than 3 galloyl units are required per galloylglucose, for precipitation, a total of more than 30 galloyl units per BSA is required.

number of three available-for-binding galloyl groups, until a "hydrophobic" coat is formed around the protein. Precipitation would commence during the second stage, once the total number of galloyl units bound to BSA reaches 30 units. The amount of precipitated BSA then increases linearly with the increase in the number of bound galloyl units until 85 units are reached, at which point complete precipitation of BSA occurs without either any cross-linking of BSA molecules by the polyphenolic entities or self-association of the polyphenols.[110]

The above polyphenol–protein association proposal is essentially driven by the hydrophobic character of the polyphenols involved in a process that globally appears to be a reversible (before precipitation) and nonspecific surface phenomenon. Even if this process applies to gallotannin-like galloylated glucose derivatives such as β-PGG, it certainly does not entirely apply to all types of polyphenols and proteins, and probably also depends on the experimental conditions used that may or may not be relevant to the conditions encountered in natural systems. One example is the relative concentrations of the protein and the polyphenol involved.[102a,106c]

As far as the type of polyphenol is concerned, Hagerman and co-workers suggested a different type of mode of precipitating complexation for proanthocyanidins (condensed tannins) on the basis of data gathered using a purified procyanidin oligomer, epicatechin$_{16}$-(4→8)-catechin (EC_{16}-C). This substance turned out to be a much more efficient BSA precipitating agent than β-PGG (ca. 20 molecules of EC_{16}-C per molecule of BSA versus 40 molecules of β-PGG per molecule of BSA).[109] Since EC_{16}-C is much more polar than β-PGG and highly hydrophilic ($K_{ow} = 2.12 \times 10^{-3}$),[109] it was proposed that it precipitated BSA by forming hydrogen-bonded cross-links between BSA molecules. It would thus seem that the hydrophilic character of the polyphenolic entity involved in protein complexation, its number of protein binding sites, and its overall size can matter after all![101d,109] In this regard, most of the literature data converge to elect water-soluble higher proanthocyanidin oligomers—especially those harboring regularly (4→8)-linked sequences—as being the best precipitators of PRPs. The multiple phenolic moieties (catechol and/or pyrogallol B rings) made available for binding by virtue of their helical threadlike shape[113] would be particularly well suited to interact in a cooperative manner with multiple sites on conformationally extended proteins,[31k,106b,109,114] notably at pH values near their isoelectric points.[97a] In contrast, tightly coiled globular proteins have much lower affinities for proanthocyanidins. This appealing shape-complementarity-dependent molecular recognition process, first proposed by Hagerman and Butler in 1981,[97a] has recently been refined by Hagerman herself and her co-workers by taking into consideration the flexibility of the protein.[114a] Thus, although *C*-glucosidic ellagitannins such as castalagin (the C1 epimer of vescalagin; see Figure 2) and grandinin have conformationally constrained structures and



are poor precipitators of the loosely structured, albeit globular, protein BSA, their relative affinities for the processed proline-rich protein gelatin were only 50% and 30%, respectively, lower than that of the flexible EC_{16}-C procyanidin.[114a] The higher flexibility of gelatin compared to that of BSA was claimed to compensate for the structural rigidity of the ellagitannins, with the protein being able to fold and wrap around the polyphenol.[98b,106a,114a]

So, both the chemical and physical features of polyphenols—for example, 1) rather hydrophobic, flat, and disclike, but flexible, such as β-PGG and gallotannins in general, 2) hydrophilic, more spherical propeller-like and rigid, such as ellagitannins, or 3) hydrophilic, elongated threadlike, and flexible, such as condensed tannins—are important parameters for determining the extent of their interactions with proteins. Of course, the same types of parameters should apply to proteins for determining the extent of their interactions with polyphenols. With these considerations in mind, match and mismatch combinations with affinities of various strengths can all be envisaged. Although studies on the precipitating complexation of some proteins with some polyphenols have generally revealed multiple interactions of polyphenols (or several molecules thereof) at the surface of proteins with dissociation constants rarely exceeding the micromolar range, more intimate and sometimes much stronger interactions are also possible—it all depends on the polyphenol and the protein at play.

Recent investigations have clearly demonstrated that polyphenols can indeed bind with strong affinity to proteins in 1:1 complexes. For example, in their efforts to understand the mechanism of inhibition of mitochondrial ATPase/ATP synthase by dietary polyphenols,[94d] Walker and co-workers obtained cocrystal structures of bovine F_1-ATPase with resveratrol, piceatannol, and quercetin (see Figure 7), and showed that these simple polyphenols block the rotary mechanism of F_1-ATPase (which is necessary for conversion of ADP into ATP) by binding to a common site in the inside

surface of an annulus made from loops in the α and β subunits of the proteins. The binding site is a hydrophobic pocket between the C-terminal tip of the γ subunit and the β_{TP} subunit (Figure 14).[115] All three bound polyphenols adopt

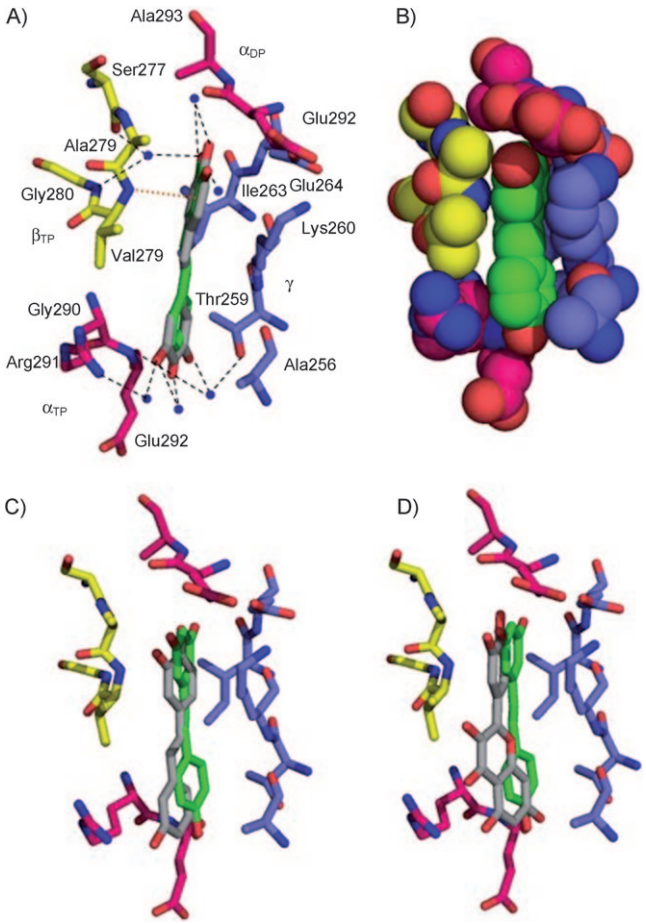


Figure 14. Binding of resveratrol, piceatannol, and quercetin to bovine F_1-ATPase. A) Side view as a stick representation (O red, N blue) showing the major binding modes (green and gray) of the interactions of resveratrol with side chains in the F_1-ATPase binding pocket. The binding-site residues shown are either within 4 Å of resveratrol and form hydrophobic interactions, or they are linked to resveratrol by H bonds (dotted lines) involving water molecules (blue spheres) and by a H bond from the amido group of Val_{279} to the π electrons of the *m*-dihydroxyphenyl moiety of resveratrol (orange dotted line). B) Same side view as in (a) in space-filling representation. C) Superimposition of resveratrol (green) and piceatannol (gray) in the binding pocket. D) Superimposition of resveratrol (green) and quercetin (gray) in the binding pocket.[115]

slightly distorted planar conformations. This mode of binding to F_1-ATPase exhibits the same basic molecular recognition features as those of resveratrol and quercetin to other functional proteins, where these polyphenols also lodge in hydrophobic pockets and establish hydrogen-bonding connections between their phenolic hydroxy groups and their surrounding amino acids.[115,116]

Among many other examples of proteins whose function is perturbed by polyphenols, the protein kinase B (Akt) has recently been shown to be a direct target for the flavonol myricetin (the pyrogallolic B-ring-bearing variant of quercetin) with a $K_D = 0.26$ μM.[117] A recent in silico study by Moro and co-workers[118] describes the identification of ellagic acid (see Figure 11), from a database of about 2000 natural products, as a potent inhibitor of casein kinase 2 (CK2); ellagic acid was shown experimentally to inhibit CK2 with a $K_i = 20$ nM.[118] Curcumin (see Figure 11) binds to the central cavity of 5-LOX, as evidenced by X-ray data on cocrystals.[119] The search for molecular targets of the bioactive tea polyphenol EGCG has recently unveiled that it binds strongly to the metastasis-associated 67 kDa laminin tumor cell receptor with a nanomolar K_D value.[120a,b] It was also found that EGCG regulates CD3-mediated T-cell leukemia receptor signaling by inhibiting the tyrosine kinase ZAP-70 with $K_D = 0.62$ μM.[120c] Rutin, the 3-*O*-glucoside of quercetin (see Figure 7), is a potent inhibitor of prostaglandin F synthase (PGFS) and, again, was shown to bind tightly to the hydrophobic active site of the enzyme. Interestingly, an X-ray crystal-structure determination of the ternary complex formed between bovine PGFS, NADPH (its cofactor), and rutin underlined the importance of stabilizing hydrogen bonds provided by the catecholic B ring of this flavonol inhibitor. In the active site, this inhibitor adopts a "U" shape, with a π-stacking interaction between this same B ring and the NADPH nicotinamide ring (Figure 15).[121]

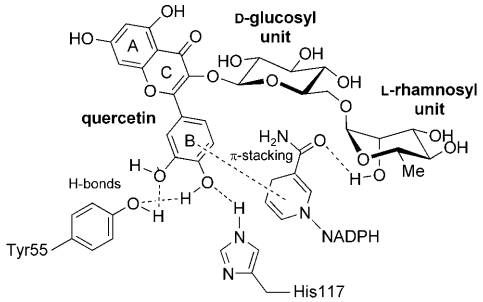


Figure 15. Key hydrogen-bonding and π-stacking interactions of rutin within the active site of bovine prostaglandin F synthase in the presence of the enzyme cofactor NADPH.[121]

The isoflavone genistein (see Figure 7) and other related so-called phytoestrogens, which have been subjected to intensive studies because of their presumed health benefits in estrogen-related problems, including breast cancer, bind to the estrogen receptor (ER).[122a] Electron density experiments have been carried out recently by Pinkerton and co-workers with the aim of better understanding how the genistein molecule approaches and binds to the estrogen receptor α (ER_α).[122b] Again, it was found that the establishment of strong hydrogen bonds between the negatively polarized oxygen atom of the OH group at the 4′-position (B ring) of genistein and the positively polarized O–H and N–H hydrogen atoms of a water molecule and an arginine residue is crucial to lock the genistein molecule into place within the ligand-binding domain of the estrogen receptor (Figure 16).[122b]

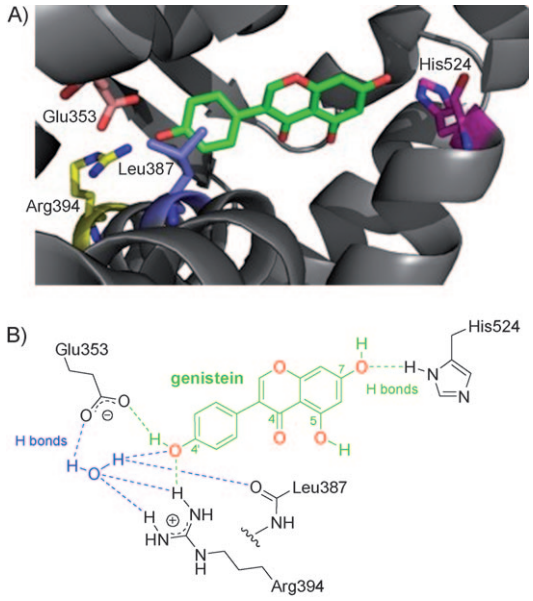


Figure 16. A) View of the binding of genistein to the estrogen receptor α($ER_α$). B) Representation of the hydrogen-bonding network of genistein within the ligand-binding cavity of $ER_α$; green dotted lines involve hydrogen bonds with genistein, and the blue ones with a water molecule, which is considered to be an important part of the receptor structure.[122b]

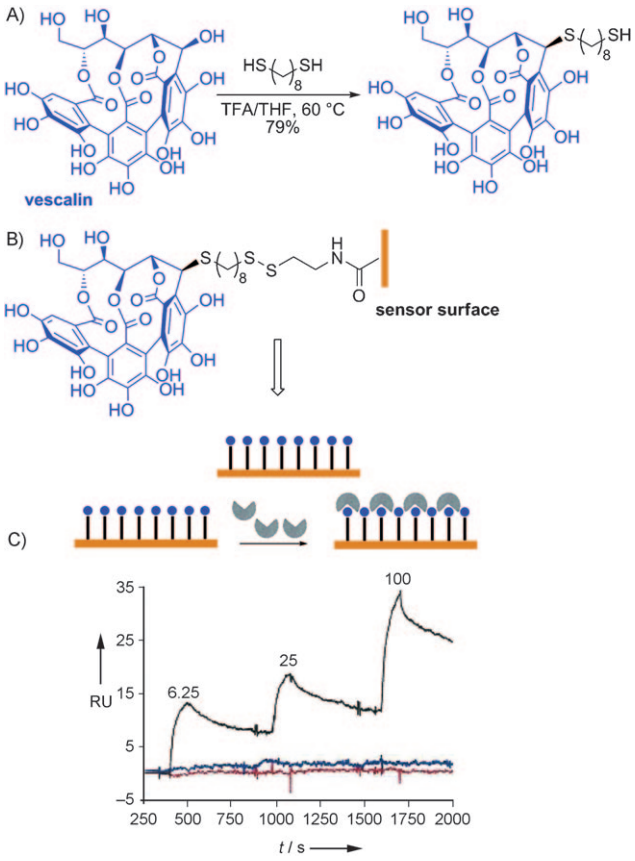


Figure 17. A) Formation of a deoxyvescalin sulfhydryl thioether derivative without the use of protecting groups. B) Its immobilization onto an SPR sensor chip surface. C) Schematic model of the binding of Top2α to the SPR surface coated with deoxyvescalin sulfhydryl thioether, and sensorgrams recorded using Top2α, BSA, and streptavidin injected at three different concentrations (6.25, 25, and 100 nM). Black line: Top2α; blue line: BSA; red line: streptavidin; RU = resonance unit.[123]

More sophisticated polyphenols such as ellagitannins have also been evaluated for their ability to bind specifically to target proteins. For example, following the tracks left by Kashiwada et al.,[88e] we reported on the efficient inhibition of human DNA topoisomerase IIα (Top2α) by several ellagitannin molecules.[65c] In particular, the *C*-glucosidic ellagitannin vescalin (see Figure 17) exhibits a much higher capacity to inhibit Top2α in vitro than etoposide (VP-16), a standard Top2α inhibitor, with a complete inhibition of DNA decatenation at 10 μM.[65c] These results prompted us to study the interaction between this polyphenol and Top2α in real time. In this context, we developed a novel analytical method based on surface plasmon resonance (SPR) spectroscopy that allows a rapid discrimination between nonspecific and specific protein–polyphenol interactions (Figure 17). This SPR-based approach relies on the preliminary attachment of the vescalin molecule onto the SPR sensor chip surface through a sulfhydryl thioether spacer, which was installed by taking advantage of the remarkable chemoselective reactivity expressed at the C1 locus of this *C*-glucosidic ellagitannin (see Figure 17 A and B). We could thus reveal the ability of vescalin to interact with Top2α with a dissociation constant in the subnanomolar range.[123] Moreover, no interaction was detected with the model proteins BSA and streptavidin, thus demonstrating the selectivity of the interaction between the immobilized vescalin molecule and Top2α (Figure 17 C).[123]

Recent studies have clearly established that not only resveratrol (see Section 3.2) but also the tea 3-*O*-galloylated flavanol EGCG exerts antifibrillogenic properties, which are of value for the fight against human protein misfolding disorders involved in neurodegenerative pathologies. For example, Wanker and co-workers showed that EGCG binds directly to natively unfolded amyloid-β (Aβ) and α-synuclein (αS) polypeptides, and hence prevents their aggregation into toxic β-sheet-rich fibrillar Aβ and αS oligomers that are implicated in the development of Alzeihmer's and Parkinson's diseases, respectively.[124] These authors proposed interesting mechanisms of the inhibitory action of EGCG against β-sheet formation (and aggregation) of αS. By preferentially binding to a highly flexible region of this peptide, EGCG would promote the rapid self-assembly of EGCG-bearing monomers into highly stable unstructured αS oligomers, thus redirecting β-sheet-forming and aggregation-prone molecules toward a different and nontoxic assembly pathway (Figure 18 A). Furthermore, EGCG-stabilized monomers and lower oligomers would not be incorporated into preformed amyloidogenic β-sheet intermediates, hence interfering with the seeded aggregation pathway to amyloidogenesis, and might thus even be able to antagonize the fibrillogenic process even after fibrils had started to accumulate (Figure 18 B).[124]

The results of the above study inspired Hauber et al. to evaluate the potential of EGCG to target a peptide fragment derived from prostatic acidic phosphatase (PAP248-286).[125a]

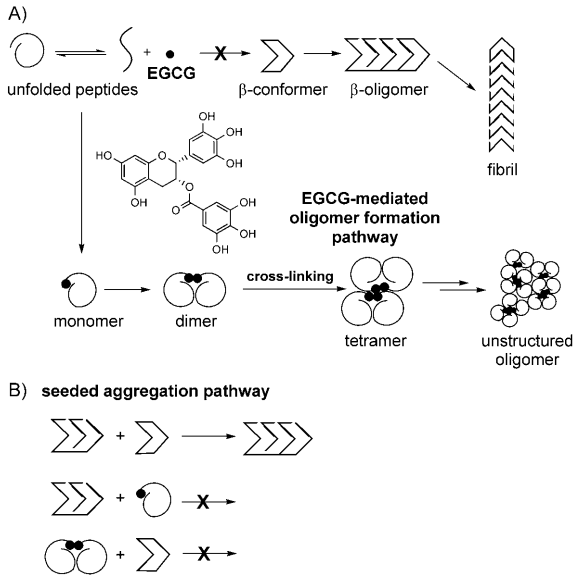


Figure 18. Models to explain the effects of EGCG on αS fibrillogenesis: A) Amyloidogenesis of monomeric polypeptides, which exist in equilibrium between unfolded and partially folded conformations, proceeds via oligomeric states to amyloid fibrils. EGCG preferentially binds to unfolded polypeptide chains and prevents amyloidogenesis by inducing the formation of unstructured, seeding-incompetent, and nontoxic oligomers. B) EGCG prevents monomer and lower oligomer addition to amyloid β-sheet intermediates, thus interfering with the seeded aggregation pathway to amyloidogenesis.[124]

This peptide is secreted in large amounts in human semen and has consistently been reported to enhance HIV-1 infection. The ability of this peptide to boost the infectivity of a broad range of HIV strains relies on its unexpected capacity to form β-sheet-rich amyloid fibrils.[125b] Hauber et al. found that EGCG is a powerful antagonist against the activity of these fibrillar structures by targeting and degrading them, thereby efficiently abrogating their HIV-1 infectivity-enhancing properties.[125a]

In related studies on the antifibrillogenic properties of EGCG, Shorter, Duennwald, and co-workers recently demonstrated that its combination with 4,5-bis-(4-methoxyanilino)phthalimide (DAPH-12), a compound known to inhibit prionogenesis, significantly improves and widens its capacity to eradicate prions. In fact, DAPH-12 was found to directly antagonize EGCG-resistant prions and to synergize with EGCG to directly inhibit and reverse the formation of diverse prion strain structures.[126] Comparison of the antifibrillogenic activity of EGCG with that of other simple polyphenols unsurprisingly unveiled that the presence of pyrogallol-type galloyl groups on rather structurally constrained polyphenols that enable specific aromatic (hydrophobic), yet hydrogen-bond-stabilized, interactions with polypeptides prone to undergo fibril formation, is the determining factor of the potency of their activity.[127] All of these investigations on the interactions between polyphenols and amyloidogenic or prionogenic polypeptides show great promise for the design of polyphenol-inspired fibrillogenesis inhibitors as therapeutic agents for the treatment of neurodegenerative diseases.[127]

4. How To Access Polyphenols?

Most simple polyphenols, such as flavonoids and certain flavanoids, are commercially available and are usually obtained in pure forms by extraction/purification from their natural sources, although biotechnological approaches to the production of some polyphenols, such as resveratrol and flavanones, have also been developed.[128] However, chemical synthesis clearly also plays an important part in accessing polyphenols in pure forms. The following discussion will focus on the most significant and recent progress that has been accomplished to access some of the more structurally challenging polyphenols by chemical synthesis.

4.1. Synthesis of Proanthocyanidic Oligoflavanols

The proanthocyanidins (condensed tannins) are composed of a myriad of oligomeric products formed by formal condensation reactions of various flavanol units by a biomechanism that has not yet been fully elucidated.[129] The high structural diversity encountered in this family of polyphenols is attributed to regio- and stereochemical variations of the flavanol interlinkages, in addition to changes in the phenolic hydroxylation pattern and in the configuration of the hydroxylated C-ring C3 center of the flavan-3-ol building block (see, for example, procyanidin dimers B_1–B_4, Figure 19). These oligoflavanols are further divided into two

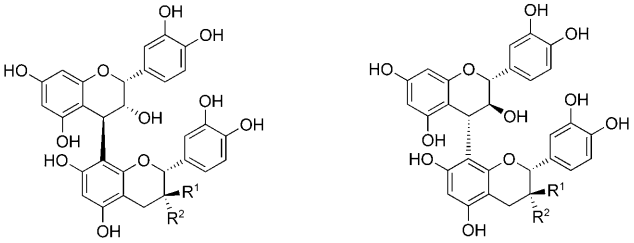
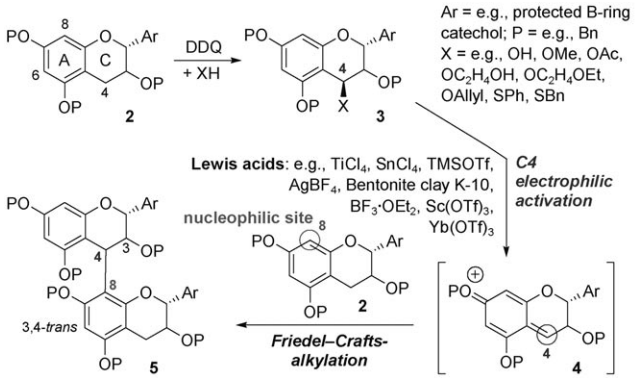


Figure 19. Structures of procyanidins B_{1-4}.

basic types, A and B, which are characterized by the occurrence of either a double or a single linkage connecting two flavanol units (see Figure 1).[12]

Although numerous investigations have indicated that the consumption of plant-derived food and beverages containing these polyphenolic materials may have beneficial effects on human health, structure–activity relationship studies aimed at delineating the details of their possible modes of action have been hampered by difficulties in isolating compounds in their pure and structurally defined forms from natural sources.[130] Consequently, intensive effort has been devoted in the last few decades to synthesize several representatives of these polyphenolic architectures. Far from being trivial, the construction of such natural products constitutes a real challenge in organic synthesis because of the difficulties in controlling the degree of oligomerization and the regio- and stereochem-

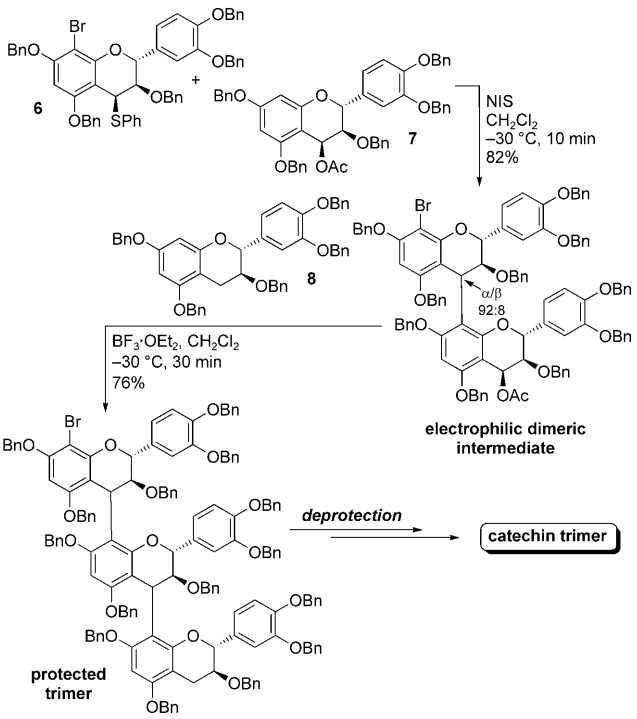
ical features of the interflavanol linkages.[12b,130] A self-condensation reaction of a flavan-3,4-diol derivative under acidic conditions could be viewed as an expeditive, and perhaps even biomimetic, solution to the problem, but it turns out not to be practical, as it inevitably produces inextricable mixtures of homooligomers.[131] Numerous stepwise-condensation approaches have been proposed since the pioneering work of Kawamoto et al. to control the formation of homooligomers, and even more challenging, that of hetero-oligomers (from different flavanol units).[132] All of these approaches are essentially based on the same Friedel–Crafts-type alkylation process to connect the benzylic C-ring C4-position of an electrophilically activated flavan-3-ol derivative with the A-ring C8 center of a nucleophilic flavan-3-ol unit (Scheme 8). Essentially limited to the synthesis of B-type



Scheme 8. Stepwise condensation for the formation of proanthocyanidin oligomers. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

oligomers composed of (4→8)-linked catechin and/or epi(gallo)catechin units, this approach first requires a flavan-3-ol derivative **3** bearing a leaving group at its benzylic C4-position. Such key building blocks are readily and stereoselectively obtained by oxidizing protected flavan-3-ols **2** with DDQ[133] in the presence of various nucleophiles (Scheme 8). The following alkylation step is most conveniently mediated by treatment of these precursors with a Lewis acid activator such as $TiCl_4$,[132,134a,b] Bentonite clay K-10,[134c] $BF_3{\cdot}OEt_2$,[131,134d,e] TMSOTf,[131,94e,132f] $AgBF_4$,[134g] or Sc(OTf)$_3$.[131] Carrying out the reaction in the presence of an excess of a C4-unsubstituted nucleophilic flavanol partner of type **2** furnishes, via transient cationic species **4** or equivalents thereof, dimers **5** (Scheme 8). A stereochemical preference for a 3,4-*trans* relationship is usually observed in the (4→8)-linked dimers thus generated, irrespective of whether the electrophilic partner **3** is derived from catechin with a β-oriented 3-OH group or from epicatechin in which it is α oriented. The nature of the Lewis acid and that of the activating substitutent at C4 play mutually important roles in controlling the extent of the stereoselectivity.[134b]

The recent scale-up production of procyanidin B_1 (see Figure 19) and its naturally occurring bis-3-*O*-gallate variant to the kilogram scale attests to the efficiency of this method,[135] which has also been employed to synthesize ^{14}C- and ^{13}C-labeled procyanidins B_2 and B_3.[136] However, in most cases, this method requires an excess of the nucleophilic partner to avoid extensive oligomerizing self-condensation reactions. Different solutions to this problem have been implemented. For example, by using the rare earth metal based Lewis acid Yb(OTf)$_3$, Makabe and co-workers recently reported the efficient synthesis of procyanidins B_{1-4} (see Figure 19), which requires only equimolar amounts of the nucleophilic and electrophilic flavanol reaction partners.[137] Suzuki and co-workers relied on capping the C8-position of the A ring of the electrophilic flavanol partner with a bromine atom. They then used an iterative orthogonal coupling strategy with differently protected/activated flavanol building blocks **6**–**8** and $BF_3{\cdot}OEt_2$ or *N*-iodosuccinimide (NIS) as activators to develop an elegant route to catechin-based oligomers (Scheme 9).[134e] This simple but quite judicious use

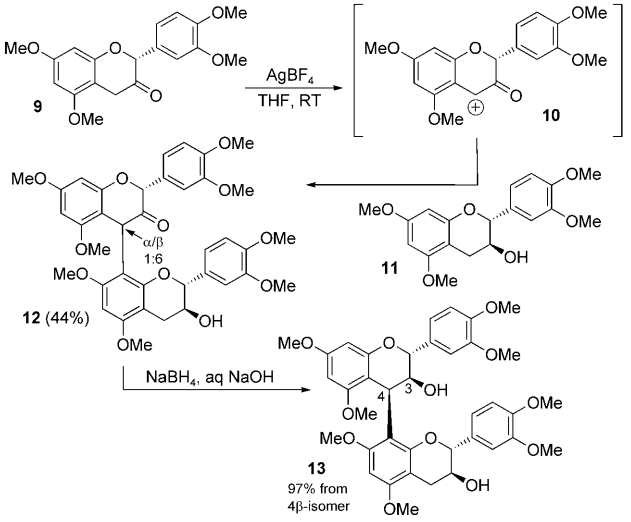


Scheme 9. Suzuki's coupling strategy for the synthesis of proanthocyanidin oligomers.[134e]

of a removable halogen atom to disarm the nucleophilic character of the C8 center of a flavanol derivative modified at C4 so as to act primarily as an electrophile has inspired other researchers in their efforts towards the synthesis of proanthocyanidins in a controlled manner.[134b]

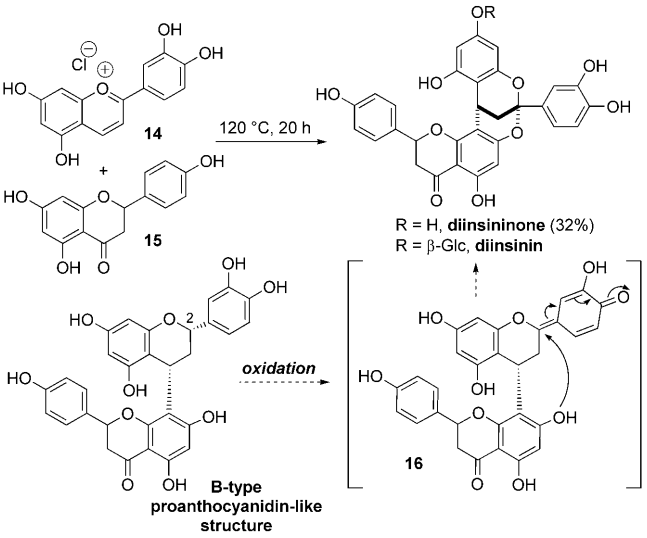
An intramolecular version of these Lewis acid mediated coupling reactions of catechin and/or epicatechin derivatives has also been reported.[138] The Lewis acid mediated stepwise condensation approach to proanthocyanidin B-type oligomers constitutes the best available route to these polyphenolic oligoflavanols today, but further improvements are still necessary to scale-up the preparation of higher oligomers in pure forms and to develop efficient access to (4→6)-linked constructs. Novel approaches are already being considered,

such as the one recently proposed by Westhuizen and coworkers, which is based on an oxidative formation of the interflavanyl bond without the need for preliminary functionalization at C4. Tetra-*O*-methyl-3-oxocatechin **9** was oxidized with an excess of the one-electron oxidant $AgBF_4$ to furnish the transient carbocation **10**, which was then trapped by the nucleophilic tetra-*O*-methylcatechin **11** to afford, after hydride reduction of the major 4β isomer **12**, the octamethylated 3,4-*cis* analogue **13** of procyanidin B_3 (Scheme 10).[139]



Scheme 10. Westhuizen's oxidative synthesis of a 3,4-*cis* analogue of procyanidin B_3.[139]

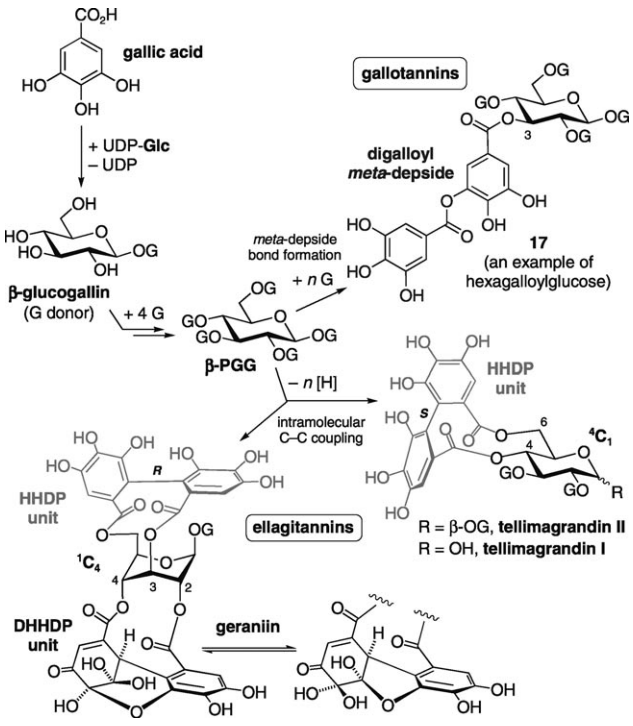
Synthetic endeavors towards A-type proanthocyanidins (for example, see the A_2 dimer in Figure 1) have been scarcer, but one example is the recent approach by Selenski and Pettus.[140] These authors reported the racemic synthesis of diinsininone, the aglycone of (±)-diinsinin, a compound discovered in the rhizome of *Sarcophyte piriei* Hutch, which inhibits prostaglandin synthesis and platelet-activating factor-induced exocytosis. A [3 + 3] coupling reaction between the benzopyrylium salt **14** and flavanone *rac*-**15** furnished *rac*-diinsininone in 32% yield (Scheme 11). Interestingly, this successful synthesis provides alternative views about the biogenesis of A-type proanthocyanidins, which had previously been proposed to entail the preliminary formation of B-type species that can be converted into A-type ones by an oxidative cyclization that requires the abstraction of their C2 hydrogen atom to form a quinone methide intermediate of type **16** (Scheme 11).[140,141]



Scheme 11. Benzopyrylium-mediated synthesis of diinsininone and presumed oxidative biosynthetic path to A-type proanthocyanidins via a quinone methide.[140,141]

4.2. Synthesis of Hydrolyzable Tannins

Hydrolyzable tannins can be considered as naturally occurring archetypes of polyphenolic clusters that adopt either disc-like or ball-like shapes. The structure of these tannins is based on a central sugar core, typically a glucose unit, to which the pyrogallolic gallic acid and/or gallic acid derived motifs are esterified. β-Glucogallin (1-*O*-galloyl-β-D-glucopyranose, see Scheme 12) is the simplest glucosyl gallate known. It serves as a galloyl unit donor in the biosynthesis of the fully galloylated β-D-glucopyranose β-PGG, which is itself considered to be the immediate precursor of the two subclasses of hydrolyzable tannins, namely gallotannins and ellagitannins.[142] Gallotannins result from further galloylations of β-PGG and are characterized by the presence of one or more *meta*-depsidic digalloyl moieties (Scheme 12). Com-



Scheme 12. Common biosynthetic filiation of gallotannins and ellagitannins. G = galloyl, UDP = uridine-5′-diphosphate.

plex gallotannins can contain up to 10, and occasionally even more, galloyl residues, as shown for gallotannins isolated from *Rhus semialata* (Chinese gall),[143a] *Quercus infectoria* (Turkish gall),[143b] and *Paeoniae albiflora* (*syn. P. lactiflora*).[143c] The hexagalloylglucose 3-*O*-digalloyl-1,2,4,6-tetra-*O*-galloyl-β-D-glucopyranose **17** is a typical gallotannin isolated from these sources. Alternatively, β-PGG can be subjected to intra- and intermolecular phenolic oxidative coupling processes that create connections between spatially adjacent galloyl residues through the formation of C–C biaryl and C–O diaryl ether bonds. The so-called hexahydroxydiphenoyl (HHDP) biaryl unit generated by intramolecular coupling is the structural characteristic that defines hydrolyzable tannins as ellagitannins. Hydrolytic release of HHDP units from ellagitannins gives rise to their facile and unavoidable conversion into the bislactone ellagic acid (see Figure 11), from which these natural products are named. It should be emphasized that the stereochemistry of the central glucopyranose core determines not only which galloyl residues can undergo C–C coupling to HHDP units, but also the nature of the atropisomeric form of these chiral biaryl motifs. Thus, the energetically preferred $^4C_1$ conformation allows the quasi-exclusive formation of (*S*)-HHDP units at the 2,3- and/or 4,6-positions, such as in the monomeric ellagitannins tellimagrandins I and II, whereas 1,6-, 2,4-, and/or 3,6-HHDPs are obtained from the less-stable $^1C_4$ conformer, for which both *R* and *S* atropisomers are observed. The structure of geraniin shown in Scheme 12 is an example of a $^1C_4$-glucopyranosic ellagitannin featuring a 3,6-(*R*)-HHDP unit. Its 2,4-HHDP unit is further oxidized to form the so-called dehydrohexahydroxydiphenoyl (DHHDP) unit, which isomerizes into an equilibrium mixture of hydrated five- and six-membered hemiketalic rings in aqueous media (Scheme 12). After more than 50 years of investigations, from the seminal work of the German chemists Schmidt and Mayer[144] to the outstanding contributions of Japanese researchers from Okayama (Okuda, Yoshida, Hatano), Kyushu (Nishioka, Tanaka, Nonaka), and Nagazaki (Kouno, Tanaka), nearly 1000 ellagitannins have been isolated from various plant sources and fully characterized to date. Their structures range from monomeric to oligomeric and complex hybrid structures.[13,84a,145] Their unusual and fascinating structures combined with their remarkable biological activities—particularly those related to their host-mediated immunomodulatory anticancer activities[146]—have intrigued a few organic chemists, who took up the formidable challenge of accessing select ellagitannins by total synthesis (see Section 4.2.2).

4.2.1. Synthesis of Gallotannins

To the best of our knowledge, despite a few chemical studies on depside motifs carried out in the early 1900s by Emil Fischer,[147] no chemical total synthesis of "complex" gallotannins (as opposed to "simple" gallotannins, namely their mono- to pentagalloylglucose precursors) has been reported so far. The chemical elaboration of *meta*-depsidic digalloyl units acylating a glucose core has been reported only by Romani and co-workers in their synthesis of the 2,3-*O*-digalloylglucose **18** (Figure 20).[148] Structure–activity relationship studies aimed at determining the influence of the gallotannin *meta*-depsidic link on the biological activities of tannins have thus mainly relied on the use of commercial tannic acid,[149] even though it is not a structurally well-defined gallotannin but rather a complex mixture of various gallotannin species and derivatives thereof.[150]

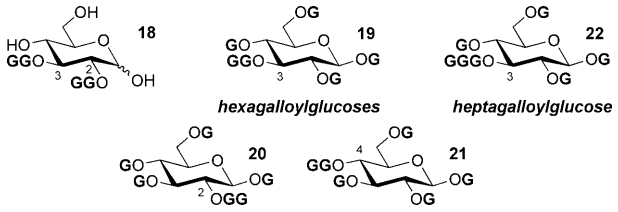
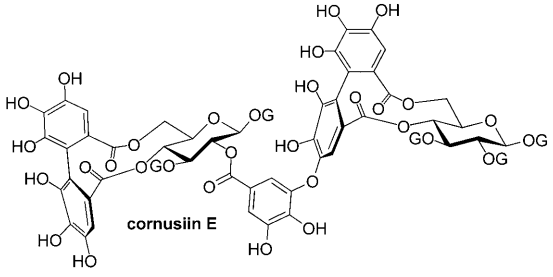


Figure 20. Selected examples of glucoses bearing *meta*-depsidic di/trigalloyl units. G = galloyl, GG = digalloyl *meta*-depside, GGG = trigalloyl *meta*-depside.

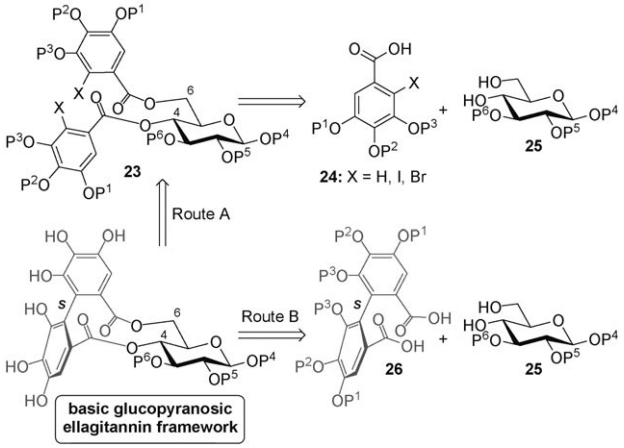
In contrast to this virtual absence of chemical synthesis of gallotannins, enzymatic synthesis has been studied intensively over the past 25 years, mainly by Gross and co-workers, with the aim of elucidating their biosynthesis. Experiments carried out in vitro with cell-free extracts from leaves of staghorn sumac (*Rhus typhina*) and β-PGG as a standard acceptor substrate led to the isolation of β-glucogallin-dependent galloyltransferases.[142a,b] It was found that none of these enzymes displayed high substrate specificity, but some of them preferentially acylated β-PGG to give the 2-, 3-, or 4-*O*-*meta*-depsidic digalloylated hexagalloylglucoses **19**–**21**, while others preferentially catalyzed the galloylation of hexa- and heptagalloylglucoses to furnish, for example, 3-*O*-trigalloyl-1,2,4,6-*O*-tetragalloyl-β-D-glucopyranose (**22**) and higher galloylated gallotannins (Figure 20).[151]

4.2.2. Synthesis of Ellagitannins

Follow-up studies led Gross and co-workers to identify in the leaves of *Tellima grandiflora* O_2-dependent laccase-type enzymes that oxidize β-PGG to the monomeric ellagitannin tellimagrandin II (see Scheme 12),[152a,b] and tellimagrandin II to its dimer cornusiin E.[152c,d]



Besides these remarkable biochemical results, outstanding progress has been accomplished in accessing ellagitannins by chemical synthesis. Several monomers and one dimeric ellagitannin of the glucopyranosic subclass have succumbed to total synthesis efforts. Two principal strategies have been developed (Scheme 13). Route A consists of a (biomimetic)



Scheme 13. Principal synthetic strategies developed for the construction of the ellagitannin framework. P^1–P^6 = protective groups.

biarylic coupling of the galloyl residues of an intermediate of type **23**, which results from an esterification of a suitably protected/activated gallic acid **24** with a diol derivative of D-glucose such as **25**. It is worth noting that the desired stereoselectivity of the coupling reaction is correctly induced by the chirality of the glucopyranose core. Atropisomerically pure (*S*)-HHDP units are thus, for example, obtained when 2,3- or 4,6-galloyl pairs on a $^4C_1$-glucopyranose are coupled together. The alternative route B relies on a double esterification of a suitably protected hexahydroxydiphenoic acid **26** with a diol derivative of D-glucose such as **25** (Scheme 13).[13b,153]

The first total synthesis of an ellagitannin natural product was reported in 1994 by Feldman et al.[154a] The 4,6-(*S*)-HHDP-containing tellimagrandin I (see Scheme 12) was synthesized by a $Pb(OAc)_4$-mediated oxidative coupling between 4-*O*- and 6-*O*-galloyl moieties of a glucose-derived intermediate according to route A (X = P^1 = H). This biarylic coupling strategy allowed the Feldman research group to achieve the total synthesis of other monomeric ellagitannins, such as the 2,3-(*S*)-HHDP-bearing sanguiin H-5 (see Figure 21),[154b] the 4,6-(*S*)-HHDP-bearing tellimagrandin II (see Scheme 12),[154c] and the 2,3-4,6-(*S*,*S*)-bis(HHDP)-bearing pedunculagin (see Figure 22), for which the 2,3-(*S*)- and the 4,6-(*S*)-HHDP units were created one after the other.[154d] Feldman and co-workers then applied route A to achieve the first successful total synthesis of dimeric ellagitannin, namely coriariin A (Figure 21).[154e,f] The key dehydrodigalloyl ether linker was prepared by a $B(OAc)_3$-mediated Diels–Alder dimerization of an *ortho*-quinone derived from methyl gallate.[37b,154c] More recently, Spring and co-workers also relied on route A to achieve another total synthesis of the $^4C_1$-

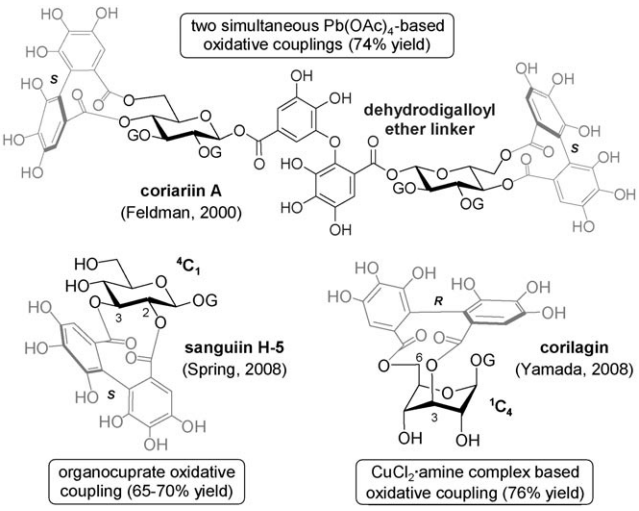


Figure 21. Selected examples of ellagitannins made by total synthesis through the biaryl coupling strategy (route A). G = galloyl.

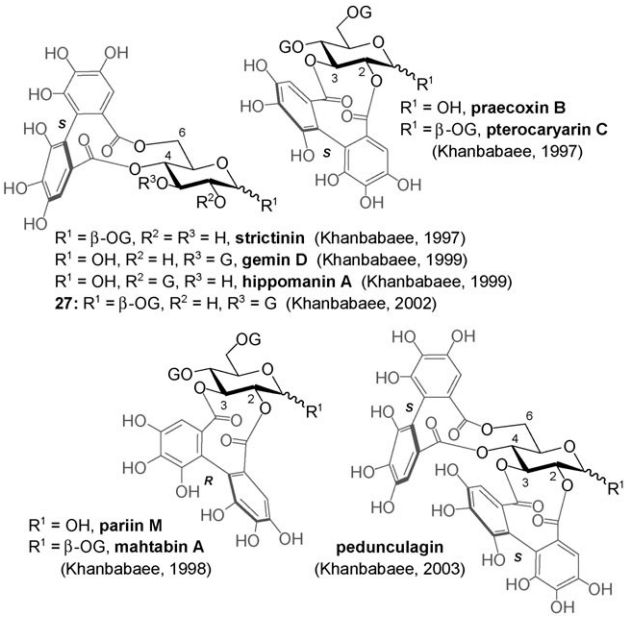
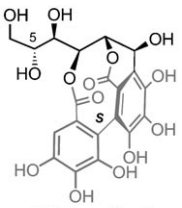


Figure 22. Selected examples of ellagitannins made by total synthesis through the HHDP bisesterification strategy (route B). G = galloyl.

ellagitannin sanguiin H-5 (Figure 21) through the use of an organocuprate oxidative intramolecular biaryl-forming reaction involving either brominated or iodinated galloyl motifs (see Scheme 13, X = I or Br).[155] Finally, in their slightly modified approach of route A (X = P^1 = P^3 = H, P^2 = Bn), Yamada et al. reported the first total synthesis of the unusual 3,6-(*R*)-HHDP $^1C_4$-ellagitannin corilagin (Figure 21) by treatment of *para*-benzylated galloyl units linked to a temporarily ring-opened sugar core with a $CuCl_2$–*n*$BuNH_2$ complex.[156]

In contrast, Khanbabaee et al. relied on (nonbiomimetic) route B using perbenzylated HHDP units, either racemic or atropisomerically pure. They achieved the total synthesis of the 4,6-(*S*)-HHDP-bearing ellagitannins strictinin,[157a]

gemin D and its regioisomer hippomanin A,[157b] the natural 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucopyranoside (**27**),[157c] as well as the 2,3-(*S*)-HHDP-containing praecoxin B and pterocaryarin C[157d] (Figure 22). Khanbabaee et al. also took advantage of this strategy to synthesize unusual (*R*)-HHDP-based ellagitannins such as pariin M and mahtabin A (Figure 22).[157e] More recently, they achieved two other total syntheses of pedunculagin (Figure 22), the bis-(*S*)-HHDP-bearing ellagitannin first synthesized by the Feldman research group,[154d] by relying on either a stepwise or a one-step twofold HHDP bisesterification strategy.[157f]



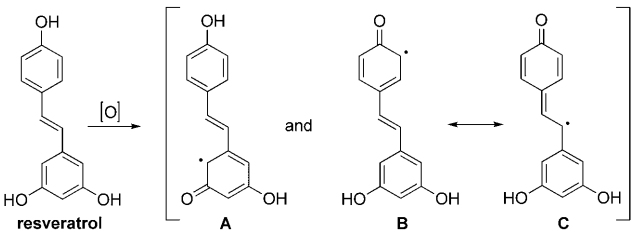
5-*O*-desgalloyl-epipunicacortein A

We also relied on such a bisesterification of a perbenzylated HHDP unit in our recent total synthesis of a first *C*-glycosidic ellagitannin, 5-*O*-desgalloylepipunicacortein A.[157g]

4.3. Synthesis of Oligostilbenes

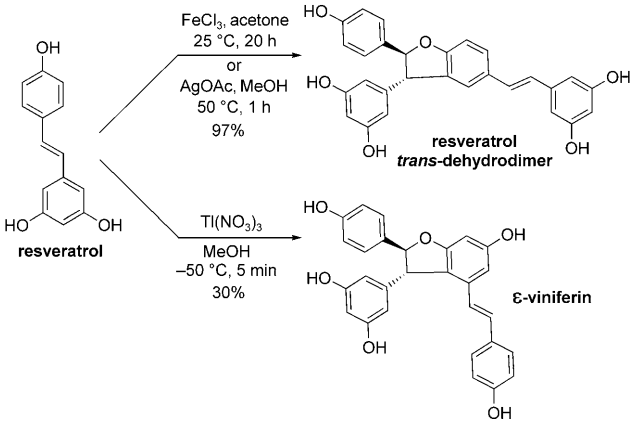
Oligostilbenes are produced by a large variety of plants including grapevines, pines, and legumes through a metabolic sequence induced in response to biotic or abiotic stress factors. These polyphenolic phytoalexins are thought to derive biosynthetically from the trihydroxystilbene resveratrol or its catecholic variant piceatannol (see Section 2.1 and Figure 9) by phenolic oxidative coupling reactions induced by enzymes such as peroxidases or laccases.[24] The high structural diversity of the oligostilbenes that results from this process is essentially due to the chemical reactivity embedded in the conjugated phenol-olefin-phenol system of the monomeric precursors, which can couple in various ways before being further transformed (bio)chemically. Since the first synthesis reported in 1941 by Späth and Kromp,[158a] several improved syntheses of resveratrol have been described that today allow the gram-scale production of this compound.[158b–d] However, relatively little effort has been devoted to the total synthesis of natural polyphenolic oligostilbenes. Two different strategies emerge from the different synthetic approaches that have been proposed in the literature. The simplest (and biomimetic) approach—although rarely the most efficient one—relies on the oligomerization of resveratrol itself by using different metal-based oxidizing chemical reagents, as well as enzymes, to produce radical or carbocationic intermediates. Dimeric oligostilbenes can be obtained in this way, but the yields are usually low, especially when using one-electron oxidants, because of the lack of firm regio- and stereocontrols in reactions mainly occuring by radical coupling processes.[159] As shown in Scheme 14, the one-electron oxidation of resveratrol furnishes several (mesomeric) carbon-centered radical species **A**–**C** that can randomly combine together to yield different kinds of dimers. This sequence is reminiscent of what is similarly proposed for the phenolic oxidative coupling of *para*-hydroxycinnamyl alcohols leading to lignins.[23]

However, some notable exceptions worth mentioning are the almost quantitative regioselective (**B** + **C**) dimerization of



Scheme 14. Carbon-centered radicals resulting from the one-electron oxidation of resveratrol.

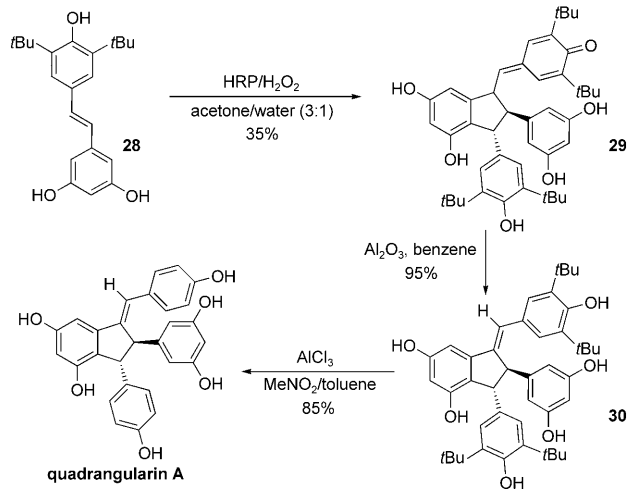
resveratrol into its *trans* dehydrodimer upon treatment with oxidants such as $FeCl_3$ or AgOAc,[159c,e] and the (**A** + **C**) dimerization into ε-viniferin in a reasonable yield of 30% by instead using the two-electron oxidant thallium trinitrate in methanol at low temperature (Scheme 15).[159c]



Scheme 15. Synthesis of resveratrol *trans*-dehydrodimer and ε-viniferin by oxidative phenolic coupling.[159c,e]

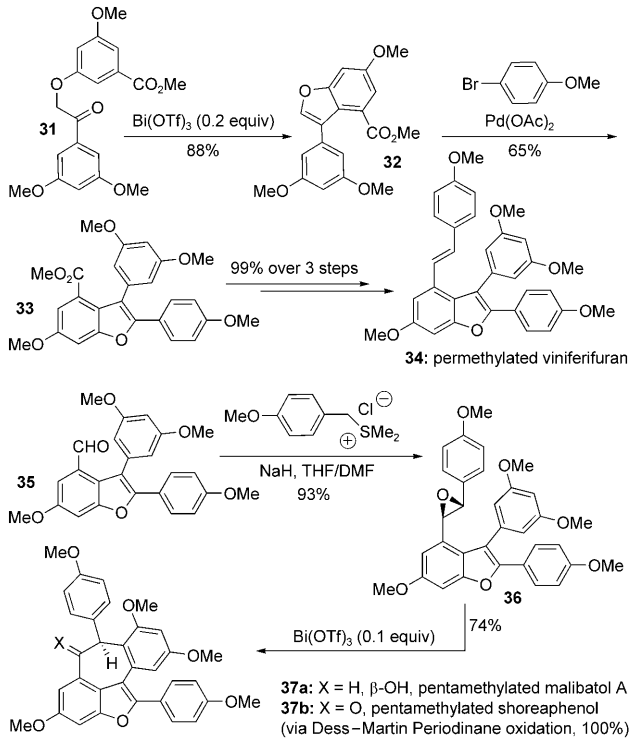
Hou and co-workers succesfully managed to synthesize the (**C** + **C**) dimer *rac*-quadrangularin A, isolated from the stem of *Cissus quadrangularis*, by using horseradish peroxidase (HRP) and hydrogen peroxide. They achieved this by blocking alternative coupling pathways by using two *tert*-butyl substituents *ortho* to the phenolic 4′-OH group of resveratrol (Scheme 16).[160] This resveratrol derivative **28** was thus oxidatively converted into dimer **29** in 35% yield. This quinone methide was aromatized after a prototropic rearrangement in the presence of Al_2O_3 to afford **30**, from which the two *tert*-butyl groups were removed using aluminum chloride to furnish *rac*-quadrangularin A in a total of 11 steps and 15% overall yield (Scheme 16).[160]

The second approach to the synthesis of oligostilbenes calls for the use of various building blocks that are different from but synthetically more controllable than resveratrol. For example, Kim and Choi recently reported the synthesis of a permethylated derivative of viniferifuran, a benzofuran stilbenoid (**A** + **C**)-type dimer analogous to ε-viniferin and first isolated from *Vitis vinifera* Kyohou, by constructing the 2,3-diarylbenzofuran core system **33** in two steps. In their approach, a regioselective $Bi(OTf)_3$-catalyzed cyclodehydra-



Scheme 16. Synthesis of quadrangularin A.[160]

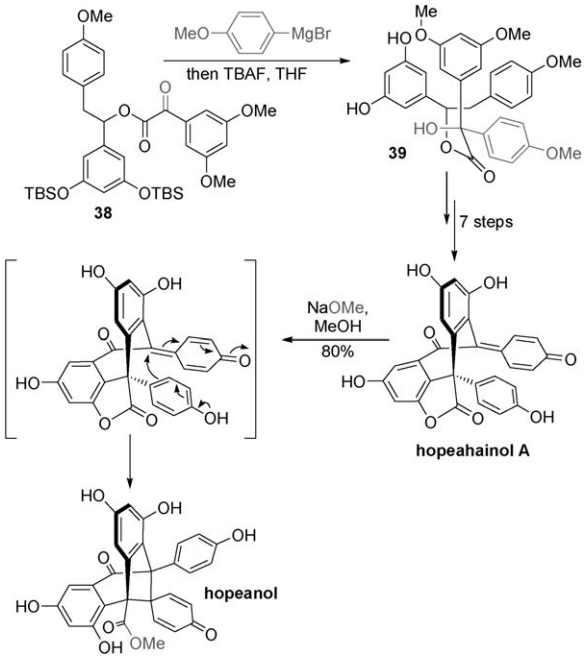
tation of the starting ketone **31** into the 3-arylbenzofuran **32** was followed by a palladium-catalyzed arylation at the C2 benzofuran center (Scheme 17).[161a] Further manipulations of



Scheme 17. Synthesis of pentamethylated polyphenols viniferifuran, malibatol A, and shoreaphenol.[161]

33, including the conversion of its ester function into an aldehyde for olefination by a classical Horner–Wadsworth–Emmons reaction, afforded the permethylated viniferifuran **34**. The aldehyde intermediate **35** was alternatively converted into the *trans*-epoxide **36** by treatment with dimethyl(4-methoxybenzyl)sulfonium chloride in the presence of NaH. $Bi(OTf)_3$ was used again to this time catalyze the opening of the epoxide and thus delivered the seven-membered ring-containing malibatol A derivative **37a**, in racemic form, which could then be easily oxidized to furnish the shoreaphenol derivative **37b**.[161a,b]

Nicolaou, Chen et al. achieved the first total synthesis of hopeahainol A and hopeanol (Scheme 18), two molecules recently isolated from *Hopea* species and exhibiting inhib-

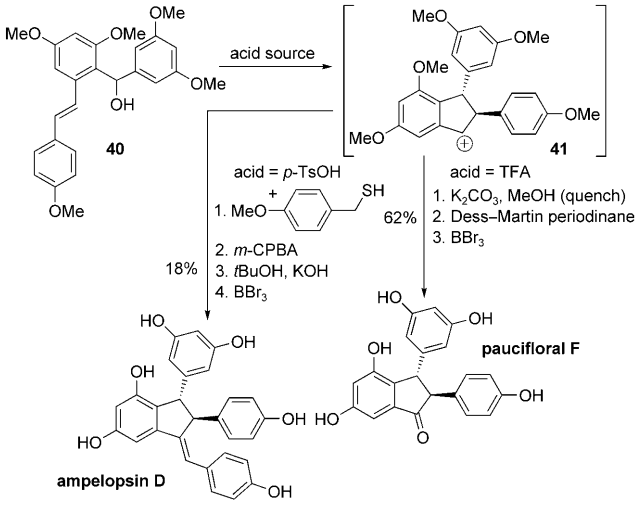


Scheme 18. Total synthesis of hopeahainol A and hopeanol.[163]

itory activity against acetylcholinesterase and antitumoral cytotoxicity, respectively, at the micromolar level.[162] The synthesis of these two resveratrol-derived dimeric compounds with an unprecedented carbon skeleton was conceived through a series of cascade reactions and a number of unusual skeletal rearrangements starting from the benzylic α-hydroxy ester **39**, which was prepared from the addition of *para*-methoxyphenylmagnesium bromide onto the keto ester **38** (Scheme 18).[163] Hopeahainol A was thus first obtained as a racemate in 17% yield over 7 steps, and efficiently converted into hopeanol in 80% yield upon exposure to NaOMe in MeOH.

This outstanding total synthesis of hopeahainol A and hopeanol by the Nicolaou research group constitutes a formidable achievement in the field of oligostilbene synthesis. In our opinion, an even more outstanding contribution was recently made by Snyder et al. They identified a common building block that is very distinct from the natural resveratrol, yet capable of being converted in a controlled manner into several of the main structural subtypes that express most of the carbogenic complexity of the resveratrol-derived family of oligomers. This was made possible by carefully orchestrated cascade reactions initiated by relatively simple reagents.[164]

The key building block **40** contains only three aryl moieties, but hence permits an easy access to some members of this family that possess an odd number of phenolic groups such as paucifloral F. Thus, by simply treating **40** with an acid source to activate its benzylic alcohol function, it was regio- and stereoselectively cyclized into the carbocationic intermediate **41**. Depending on the nature of the nucleophilic part of the acid used, either paucifloral F was produced in 62% yield over three steps or ampelopsin D was generated in 18% yield over four steps (Scheme 19). Simple modifications of **40**



Scheme 19. Total synthesis of paucifloral F and ampelopsin D.[164]

led to three additional building blocks featuring veratryl moieties with different placements of the mono- and dimethoxylated phenyl rings relatively to those in **40** (see **42** in Figure 23). With these starting materials and a few standard chemical reagents, Snyder et al. accomplished the formidable task of producing 11 natural products and 14 analogues thereof featuring five-, six-, or seven-membered rings, as well as [3.3.0]-, [3.2.1]-, and [3.2.2]-bicycles (Figure 23).[164a]

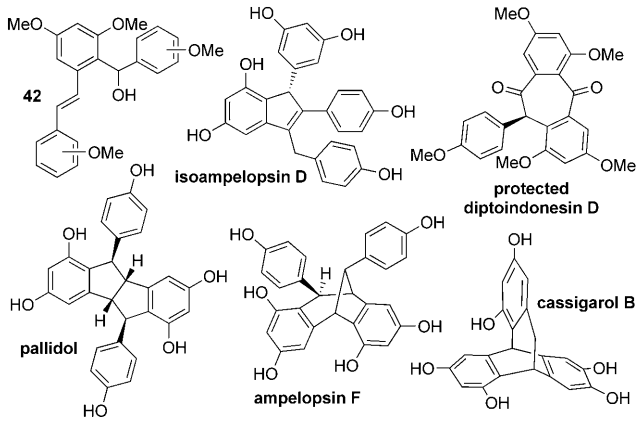


Figure 23. Snyder's key building blocks and a selection of typical oligostilbenes synthesized from them.[164a]

5. What About the Future? Remaining Challenges ...

Investigations on plant polyphenols concern so many different scientific domains that numerous challenges inevitably still lie ahead. Despite the outstanding progress that has been accomplished to access polyphenols in pure forms by chemical synthesis, organic chemists can still find many challenging targets in the various families of plant polyphenols to express their talents for making complex natural products and analogues thereof. The need for new synthetic compounds is particularly important for fueling structure–activity relationship studies aimed at understanding the modes of action of the most biologically active members of these classes of natural products. The biosynthesis of certain polyphenols will also keep biochemists, molecular biologists, as well as organic chemists busy. Particularly important is delineating the final steps of the biogenesis of proanthocyanidins and anthocyanins, which still today resist complete elucidation, and identifying many as yet unknown polyphenol-making enzymes. Moreover, plant polyphenols that have been, and still are, so much acclaimed for their role as potent antioxidants when present in food and beverages seem to be in fact—according to literature data—primarily used by plants as metabolites that are capable of being readily oxidized into reactive quinonoid species, which are susceptible to covalently modify biomolecules of foreign and pathogenic origins. It is perhaps on this aspect that more investigations on the biological activity of polyphenols should focus. Indeed, if a chemopreventive action against various human diseases by dietary polyphenols and other plant-derived phenolics can be attributed to their role as general antioxidants that are capable of quenching toxic free radicals generated from biomolecules such as lipids, proteins, and nucleic acids under oxidative stress conditions, a conceivable chemotherapeutic action could also be exploited for the development of polyphenol-based "prodrugs" against diseases such as cancer on the basis of the capability of polyphenols to generate toxic quinonoid species and to act as pro-oxidants under certain conditions. In this context, growing evidence suggests that cancer cells in general are under increased oxidative stress and are consequently characterized by a higher level of ROS concentrations compared to normal cells. Thus, this calls for the development of therapeutic substances capable of taking advantage of this higher ROS level, and even of further increasing it, to preferentially kill cancer cells without affecting the proliferation of normal cells.[63,165] Plant polyphenols have all the main requisite physicochemical properties to become such therapeutic substances with cancer-cell-selective cytotoxic activities!

Even if most of the data collected from bioavailability studies on dietary polyphenols have caused a global disappreciation of their potential benefits for human health, we could argue that many scientists who have undertaken these investigations might have been barking up the wrong tree. We agree that most dietary polyphenols are weakly absorbed and rapidly metabolized, but they could still exhibit valuable effects in the long-term prevention of those diseases that develop over a long period of time, by being present in the

organism at the low but constant doses provided by a regular dietary intake.

Furthermore, it is today quite clear that polyphenols are not just capable of precipitating proteins in an indiscriminate manner, but that many of them can interact with various molecular targets, which affect signaling pathways within cells in different ways, engage functional proteins in the formation of inhibiting complexes of strong affinities, or perturb the association of certain proteins into toxic supramolecular arrangements. If many plant polyphenols are indeed missing a few qualifications to become pharmaceutical drugs because of their poor oral bioavailability and overall lack of adherence to Lipinsky's stringent "rule of 5",[166] medicinal organic chemists can still elaborate the best possible analogues, as they often do when developing drugs directly derived from natural products. The design of novel polyphenol-based or polyphenol-inspired drugs against specific protein targets thus constitutes another promising direction for future research on polyphenols. Plant polyphenols have already started to inspire academic scientists in their quest for novel anticancer agents, more powerful natural product-like antioxidants for use, for example, as food preservatives, and antifibrillogenic agents for the fight against neurodegenerative pathologies, as well as various functionalized materials that take advantage of the unique physicochemical properties of the phenol functional group.[167] Many more exciting developments are certainly around the corner.

Let's conclude this Review with a few last words on (red) wine, that unique and pleasing-to-the-taste cocktail of polyphenols. A large dose of proanthocyanidins (and anthocyanins), a squeeze of flavonols and ellagitannins, a zest of resveratrol… After having read about all of the health-promoting effects apparently expressed by these different polyphenols, one could be tempted to view wine as the universal remedy offered to humankind by Panacea and Dionysos. However, like with any other kind of remedy, consumption should of course be kept moderate … Let's also recall that historical anecdote about Désiré Cordier (1858–1940), founder of the Cordier wine trading house in Bordeaux, who organized, in Saint-Julien-Beychevelle (Médoc, France) in 1934, the first "longevity festival", after having noted that life expectancy in this wine-producing area near Bordeaux was 45% higher than the national average … A votre santé!

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