Generalities

Phenolics form a vast group of substances which is difficult to define in simple terms. The fundamental structural element that characterizes them is the presence of at least one aromatic ring substituted by at least one hydroxyl group, free or engaged in another function: ether, ester, or glycoside. However, a purely chemical definition of phenols is insufficient to characterize plant phenolics: it would include secondary metabolites which possess these structural elements, but which evidently belong to quite different phytochemical groups. For example, many alkaloids (e.g., boldine, morphine) and a fair number of terpenes (e.g., thymol, gossypol, carnosol) have, within their structure, an aromatic ring and a phenolic hydroxyl group! This is why a biosynthetic criterion is necessary to better define the boundaries of the group.

Only plants and microorganisms are capable of biologically synthesizing the aromatic nucleus. Animal organisms are almost always dependent on either their nutrition or a symbiosis to elaborate indispensable metabolites* comprising this structural element (e.g., amino acids, vitamins, pigments, toxins).

Plant phenolics arise from two main aromatization pathways:

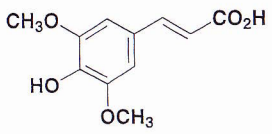
– the most common pathway is the one which, via shikimate (shikimic acid), leads from monosaccharides to aromatic amino acids (phenylalanine and tyrosine), then, by deamination of the latter, to cinnamic acids and their numerous derivatives, including benzoic acids, acetophenones, lignans, lignins, and coumarins;

* there are a few exceptions, such as estrogen hormones

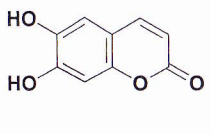
– the other pathway begins with acetate and leads to poly-β-ketoesters of variable length—polyketides—which afford, by cyclization (Claisen or aldol condensation), products that are often polycyclic, including chromones, isocoumarins, orcinols, depsides, depsidones, xanthones, and quinones.

The structural diversity of phenolics is due to this dual biosynthetic origin and is increased by the frequent combination of the shikimate and acetate pathways in the elaboration of compounds of mixed origin (e.g., flavonoids in the broad sense of the term, stilbenes, pyrones, and xanthones). The participation of a third elementary synthon—mevalonate—is also possible, although less frequent, and results in mixed derivatives of shikimic acid and mevalonate such as certain quinones or furano- and pyranocoumarins, or in mixed compounds from acetate and mevalonate such as cannabinoids. In a few cases, all three precursors contribute to the elaboration of one structure, for example that of rotenoids.

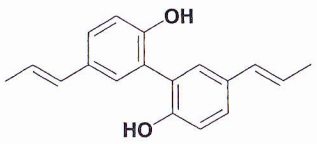
Classically, amino acid derivatives that retain the nitrogen atom are considered alkaloids or related substances (e.g., aromatic amines, betalains). In the same fashion, some mono-, sesqui-, and diterpenes can undergo partial desaturation and have a phenolic hydroxyl: yet they are considered terpenes, because aromatization is only a secondary process.



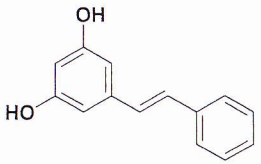
Sinapic acid
PHENYLPROPANOIC ACID



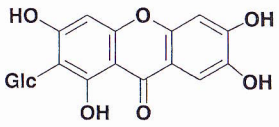
Aesculetin
COUMARIN



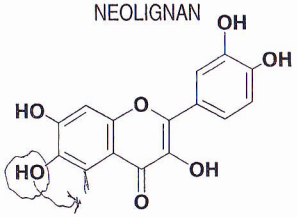
Magnoliol
NEOLIGNAN



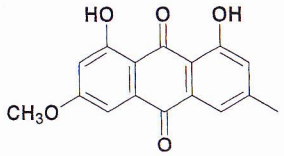
Pinosylvin
STILBENE



Mangiferin
XANTHONE

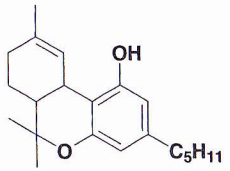


Quercetin
FLAVONOL



Physcion

Xanthoxylin



THC

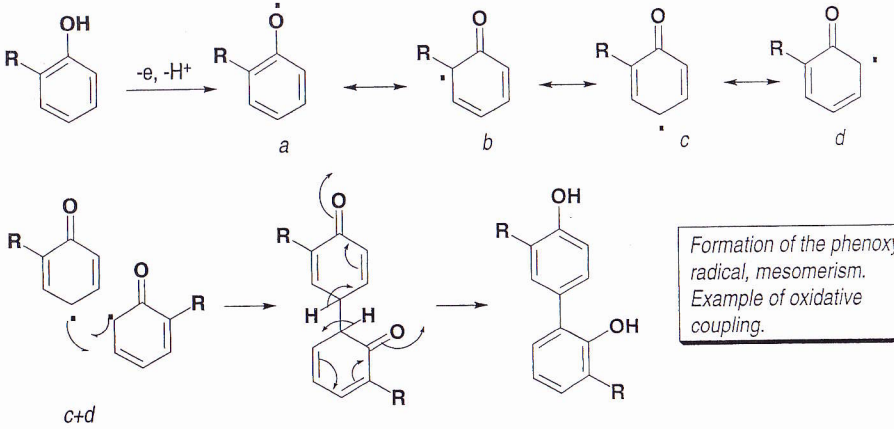
Hopefully, these comments help clarify the concept of plant phenolic: a compound devoid of nitrogen, whose aromatic ring(s) arose chiefly from the metabolism of shikimic acid, or that of a polyacetate, or both.

The great structural diversity of phenolics makes it difficult to give an overview of the methods of extraction and isolation, the processes at play during their biosynthesis, and their physico-chemical and biological properties. Therefore, these compounds, and the drugs containing them, will be discussed in groups designed on the basis of their biosynthetic origin and according to the following outline:

- "shikimates" (shikimic acid derivatives) and drugs containing them;
  - . 1-phenylpropane derivatives,
  - . 1-phenylpropane chain elongation derivatives,
- "polyketides" * (compounds arising chiefly from the cyclization of a poly-β-ketoester) and drugs containing them.

1. HOMOLYTIC CLEAVAGE

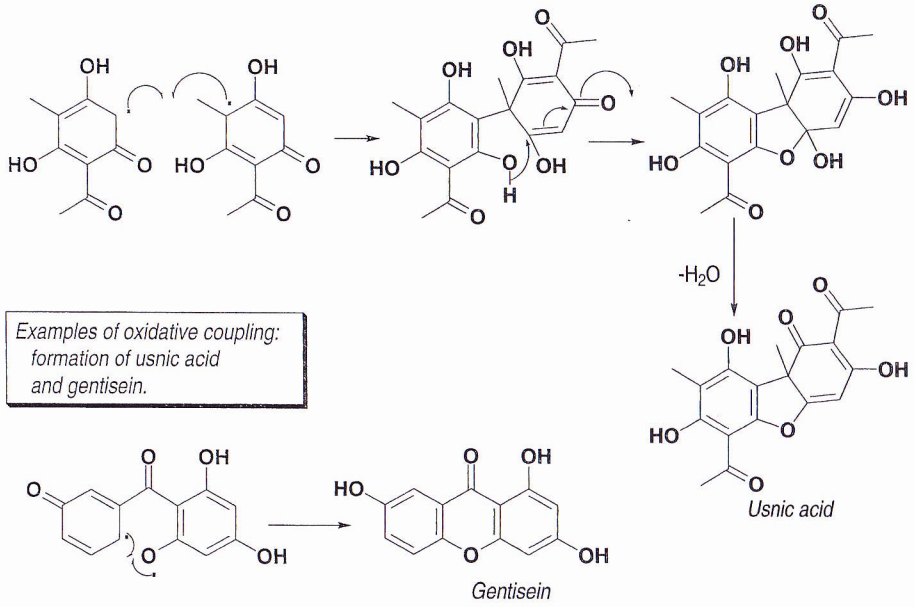
Oxidation of the phenolate ion is facile and yields a phenoxy radical which is stabilized by resonance and highly reactive. This ease of oxidation has consequences in the domains of analytical chemistry (e.g., color reactions with ferric chloride), pharmaceutical technology (instability, incompatibilities with metals), and practical applications (antioxidant and radical scavenging properties). In addition, the facile formation of phenoxy radicals and their coupling are directly involved in many biosynthetic processes (as illustrated by the formation of usnic acid or xanthones, see figure).



Formation of the phenoxy radical, mesomerism. Example of oxidative coupling.

* The term polyketide is used here in a limited sense excluding linear polyacetates (fatty acids

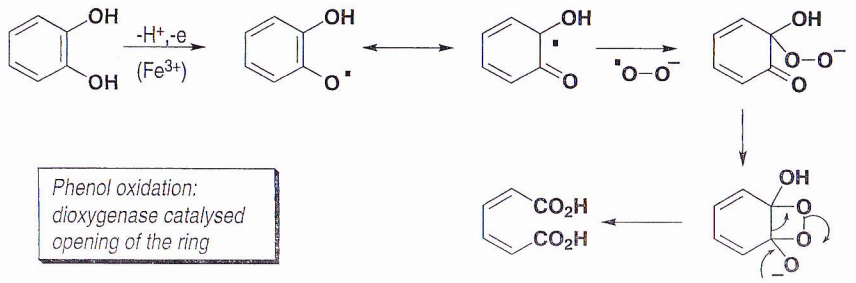
This reaction—phenolic oxidative coupling—affords biphenyl linkages or diphenyl ether linkages. It may be intramolecular (formation of new rings) or intermolecular (this is one of the known biosynthetic pathways toward polymers). This reaction occurs commonly in the biosynthesis of phenolics (see metabolism of polygalloylglucoses, lignans, and lignins), and other metabolites (see isoquinoline alkaloids).



Examples of oxidative coupling: formation of usnic acid and gentisein.

2. OXIDATION OF THE AROMATIC RING

Phenol oxidation is a common occurrence during biosynthetic processes. It may lead to either cleavage or to hydroxylation of the aromatic ring. In the first case, the reaction is catalyzed by a dioxygenase which, in the presence of ferric salts, incorporates both oxygen atoms of the oxygen molecule. In the second case, the reaction is catalyzed by a monooxygenase which incorporates into the aromatic compound only one oxygen atom, the other atom being reduced by an appropriate



Phenol oxidation: dioxygenase catalysed opening of the ring

donor (AH_2). The mechanism of this hydroxylation involves an arene oxide which opens with concurrent proton migration ("NIH shift", first described by a National Institutes of Health researcher, see specialized texts).

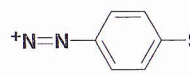
3. ACIDITY OF PHENOLS

Phenolate ion stabilization by resonance explains the acidity of these molecules: consequently, they are soluble in alkaline hydroxide solutions. It also explains why they are so highly reactive.

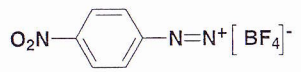
4. CHARACTERIZATION OF PHENOLICS

Some phenolic compounds are directly visible, such as flower anthocyanins, and others can be visualized under ultraviolet light (directly or after exposure to ammonia vapors) or by color reactions. The latter are used preferably after chromatography of an ethanolic extract: a direct search on the extract would have little significance because of the numerous substances that may interfere; the same comment applies to the observation of fluorescence. General reagents for phenols abound: ferric chloride, phosphomolybdate-phosphotungstate, vanillin and other aldehydes in the presence of hydrochloric acid, 4-diazoniobenzenesulfonate followed by sodium carbonate, 4-nitrophenyldiazonium tetrafluoroborate followed by sodium acetate (to form colored azobenzenes or styrylazobenzenes), and 2,6-dichloroquinone chlorimide (Gibbs reaction and formation of indophenolates). For some of the reagents, the phenolic structure determines a certain specificity, the reaction rate, and the resulting color, and lends to the reaction a diagnostic value which is not absolute, but should not be neglected.

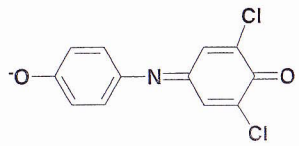
Two-dimensional paper chromatography remains a good routine means of identification of the main groups of phenolics present in the alcoholic extract of a drug. The method may be combined with TLC analysis of the hydrolysis products in the presence of hydrochloric acid, that of lipophilic phenols, and with electrophoresis of charged molecules (for example, anthocyanins or flavonoid sulfates).



4-Diazoniobenzenesulfonate



4-Nitrophenyldiazonium tetrafluoroborate



Indophenolate (Gibbs test)