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# Phenolic Compounds: Classification, Chemistry, and Updated Techniques of Analysis and Synthesis

*Hamad H. Al Mamari*

## Abstract

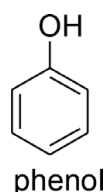
Phenolic compounds are vast, diverse, ubiquitous and widespread in nature. The biological significance of bioactive phenolic natural secondary metabolites is immense and of high and significant importance. Phenolic compounds are known to exhibit various biological activities such as antimicrobial, antioxidant and anti-inflammatory properties. This book chapter begins with classification of phenolic compounds in concise manner followed by going through their chemical properties that are essential for their biological activities. Some chemical properties such as acidity and formation of radicals are directly linked with their important and key biological activities such as antioxidant properties. The chapter covers methods and updated techniques of analysis of phenolic compounds. Finally, biosynthesis of such important organic molecules is covered going through some of their current synthesis methods in the laboratory, methods of their synthetic elaboration. Due to the high potential of phenolic compounds for applications in various industries such as pharmaceutical and food industries, the search for the development of efficient methods for their synthesis as well as modern and accurate methods for their detection and analysis will continue.

**Keywords:** Phenolic compounds, chemistry of phenolic compounds, biosynthesis of phenolic compounds, phenolics, classification of phenolic compounds

## 1. Introduction

Phenolic compounds are a diverse class of bioactive secondary metabolites and are of high and significant importance. [1–7] They can be described as compounds that contain a phenol moiety. Phenol itself is a benzene ring that is substituted with a hydroxyl group (**Figure 1**). Thus, its systematic name is hydroxybenzene.

Phenolic compounds display a wide range of biological activities. For instance, they are known to exhibit antioxidants, antimicrobial, and anti-inflammatory properties. They are ubiquitous in nature. For instance, they are present in various types of fruits such as apple, banana, orange, mango, peach, papaya, strawberry, pomegranate, watermelon, and pineapple. For example, myricetin (a flavonol) is found in apple, gallic acid (a hydroxybenzoic acid) is found in banana, quercetin (a flavonol) and cyanidin (an anthocyanin) are found in pomegranate, *p*-coumaric



**Figure 1.**  
*The structure of phenol.*

acid (a hydroxycinnamic acid) and naringenin (a flavanone) are found in orange, vanilic acid (a hydroxybenzoic acid) and resveratrol (a stilbene) are found in strawberry, ferulic acid (a hydroxycinnamic acid) and apigenin (a flavone) are found in mango, and luteolin (a flavone) is found in watermelon and pineapple. [8] The health benefits of phenolic compounds are immense. Since original research articles and reviews on phenolic compounds are numerous in the literature, this chapter is not intended to be a comprehensive review of phenolic compounds. It is rather an attempt to complement existing article and reviews and to serve as a brief reference on their classification, analysis, chemistry, and synthesis.

## 2. Classification

Phenolic compounds can generally be classified into simple and polyphenolic compounds. [9–12]

### 2.1 Simple phenolic compounds

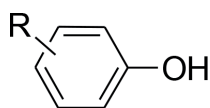
Phenolic compounds that contain one phenol unit (or a derivative of it) are considered “simple”. Fundamentally, they are substituted phenol compounds. Simple phenolic compounds have  $C_6$  general skeleton representation. The general structure is shown below (**Figure 2**). The group denoted by “R” (an organic group which could be alkyl, alkenyl, aryl ...etc. or hydroxy, alkoxy, amino ...etc) which can be in the *ortho* (*o*), *meta* (*m*), or *para* (*p*) positions of the aromatic ring. These descriptors refer, with respect to the position of the hydroxyl group constituting phenol which is given position 1, to 1,2-, 1,3, and 1,4-carbon relationship respectively.

Below are some simple phenolic compounds.

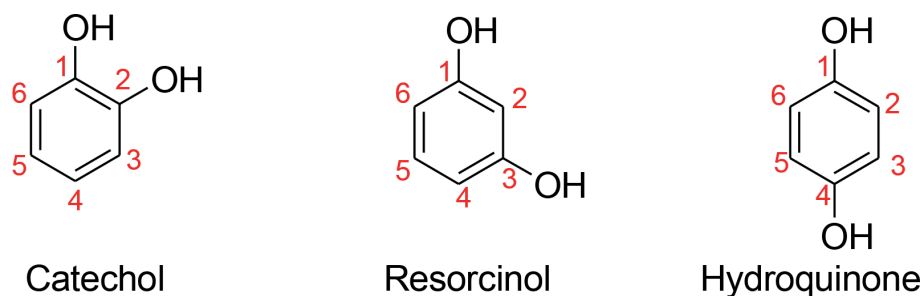
#### 2.1.1 Simple phenolics

Simple substituted phenol compounds can be hydroxyphenols or dihydroxybenzenes. Examples are catechol (1,2-dihydroxybenzene), resorcinol (1,3-dihydroxybenzene), and hydroquinone (1,4-dihydroxybenzene) (**Figure 3**).

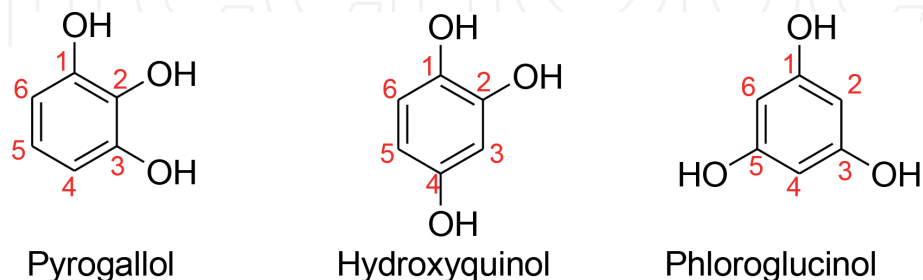
Other simple substituted phenol compounds can also be dihydroxyphenols or trihydroxybenzenes. Examples are pyrogallol (1,2,3-trihydroxybenzene), hydroxyquinol (1,2,4-trihydroxybenzene), and phloroglucinol (1,3,5-trihydroxybenzene) (**Figure 4**).



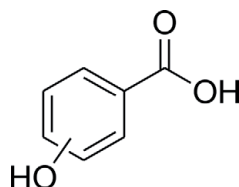
**Figure 2.**  
*General structure of simple substituted phenols.*



**Figure 3.**  
The structure of hydroxyl-substituted phenols.



**Figure 4.**  
The structure of dihydroxyl-substituted phenols.



**Figure 5.**  
General structures of hydroxyl-substituted benzoic acids.

### 2.1.2 Phenolic acids

Phenols that contain a carboxylic acid are termed as phenolic acids. If the carboxylic acid functional group is directly bonded to the phenol ring, the phenolic compound is termed as hydroxybenzoic acid. When carboxylic acid functional group and the phenol ring are separated by two doubly bonded carbons (a C=C bond), phenolic compounds are termed as hydroxycinnamic acids.

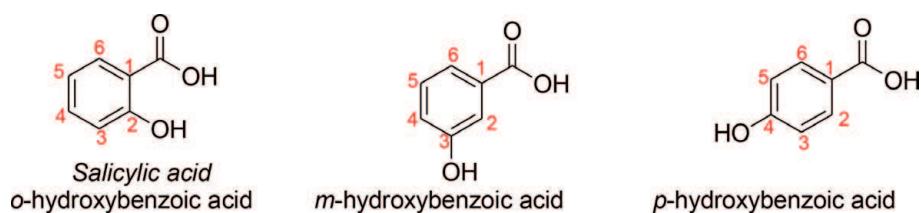
#### 2.1.2.1 Hydroxybenzoic acids

Hydroxybenzoic acids are benzoic acids substituted with a hydroxyl group. Alternatively, they can be viewed as phenols that are substituted with a carboxylic acid functional group that is directly bonded to the phenol ring (**Figure 5**).

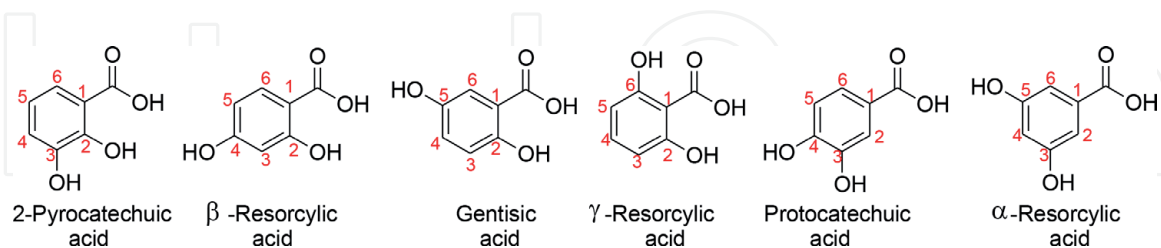
The hydroxyl group in hydroxybenzoic acids can be *ortho* (*o*) (salicylic acid), *meta* (*m*), or *para* (*p*). The structures are shown below (**Figure 6**).

Dihydroxybenzoic acids are benzoic acids that are substituted with two hydroxyl groups. The two hydroxyl groups can mainly be in 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5- relative positions (**Figure 7**).

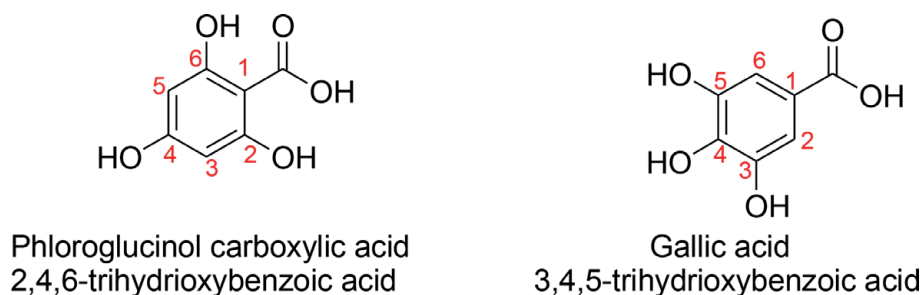
Trihydroxybenzoic acids are benzoic acids that are substituted with three hydroxyl groups. Examples include 2,4,6-trihydroxybenzoic acid and 3,4,5-trihydroxybenzoic acid (gallic acid) (**Figure 8**).



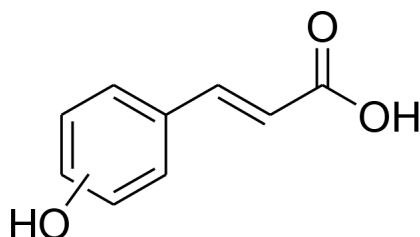
**Figure 6.**  
Structures of hydroxybenzoic acids.



**Figure 7.**  
Structures of main dihydroxybenzoic acids.



**Figure 8.**  
Examples of trihydroxybenzoic acids.



**Figure 9.**  
General structures of hydroxyl-substituted cinnamic acids.

#### 2.1.2.2 Hydroxycinnamic acids

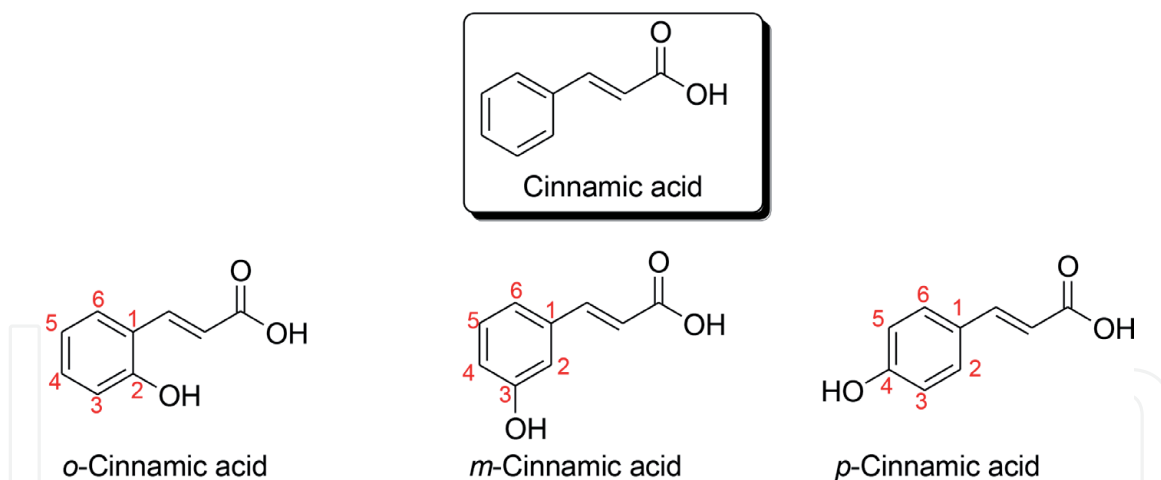
When the carboxylic acid functional group is separated from the phenol ring by a C=C bond, phenolic acids are described as hydroxycinnamic acids (**Figure 9**).

Examples of hydroxycinnamic acids are 2-, 3-, and 4-hydroxycinnamic acid shown below (**Figure 10**).

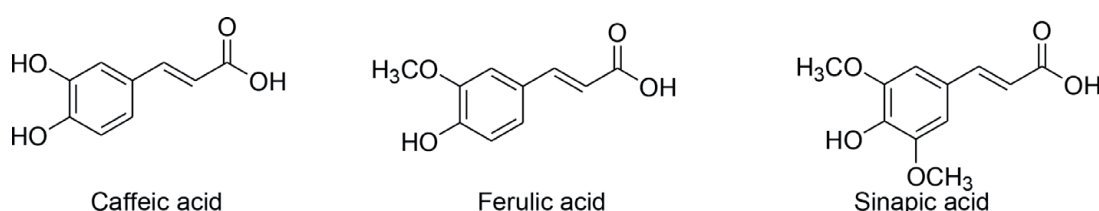
Other common examples of cinnamic acids are caffeic acid, ferulic acid, and sinapic acids shown below (**Figure 11**).

#### 2.1.2.3 Coumarins

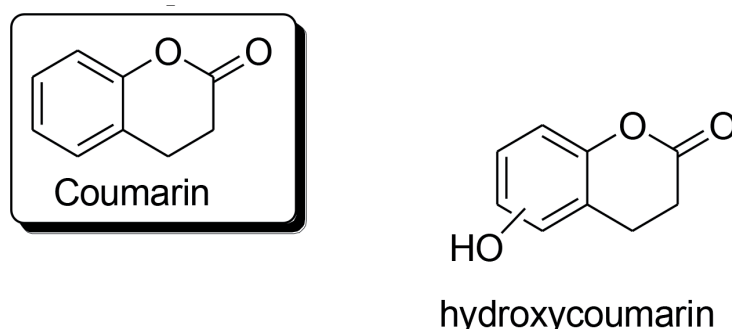
Hydroxycoumarins are hydroxyl-substituted coumarins (**Figure 12**). They are examples of phenolic compounds.



**Figure 10.**  
*Examples of hydroxycinnamic acids.*



**Figure 11.**  
*Common examples of hydroxycinnamic acids.*



**Figure 12.**  
*General structure of hydroxycoumarins.*

Examples of hydroxycoumarins are scopoletin and auraptene (**Figure 13**).

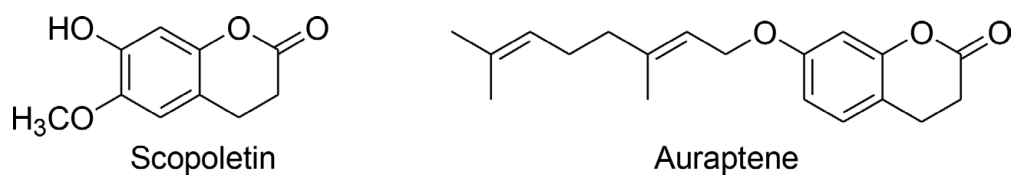
## 2.2 Polyphenols

Phenolic compounds that contain more than one phenol unit are considered “polyphenol”. Polyphenolic compounds have C<sub>15</sub> general skeleton representation.

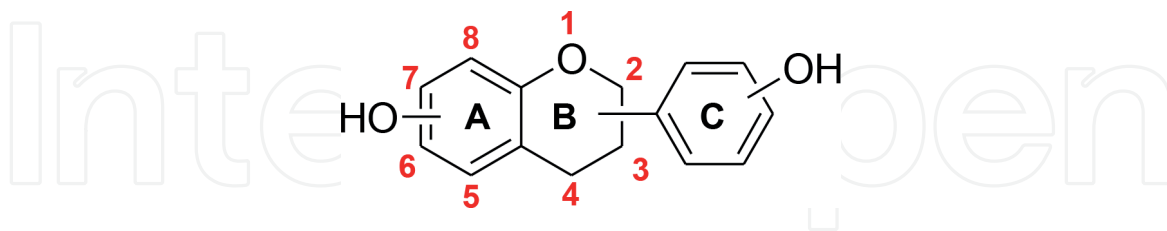
### 2.2.1 Flavonoids

Flavonoids are polyphenolic compounds with the general structure shown below (**Figure 14**).

Generally, rings A and C are either mono, di, or trihydroxylated. The *O*-heterocycle B is usually a pyrone ring as in Luteolin but could also be a pyrlium ring as in delphinidin (**Figure 15**). If ring C is attached to C2 of ring B, the flavonoid is a flavone (as Luteolin), flavonol (as kaempferol), an anthocyanin (as delphinidin) or a flavanone (as naringenin). If the ring C is attached to C3 of ring B, then



**Figure 13.**  
Examples of hydroxycoumarins.



**Figure 14.**  
General structure of flavonoids.

Class	General structure	Example	Class	General structure	Example
Flavone			Anthocyanin		
Flavonol			Flavanone		
Chalcone			Isoflavone		

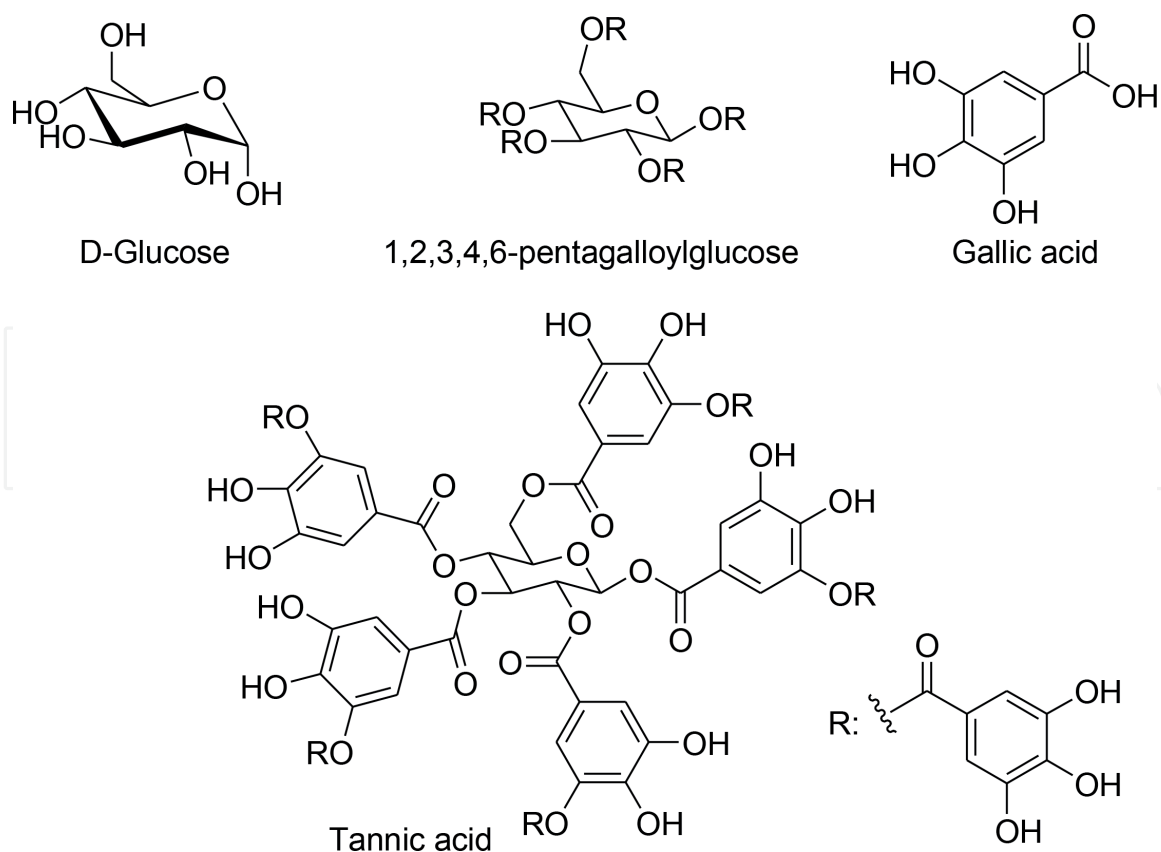
**Figure 15.**  
Classification of flavonoids.

the flavonoid is an isoflavone such as daidzein. Chalcones such as chalcone, are a class of flavonoids in which rings A and C are separated by 3-carbon linear chain rather than a ring. The bond between C2 and C3 of ring B is commonly double as in flavones, flavonols, chalcones and isoflavones. However, the C2-C3 bond could be single as in flavanones.

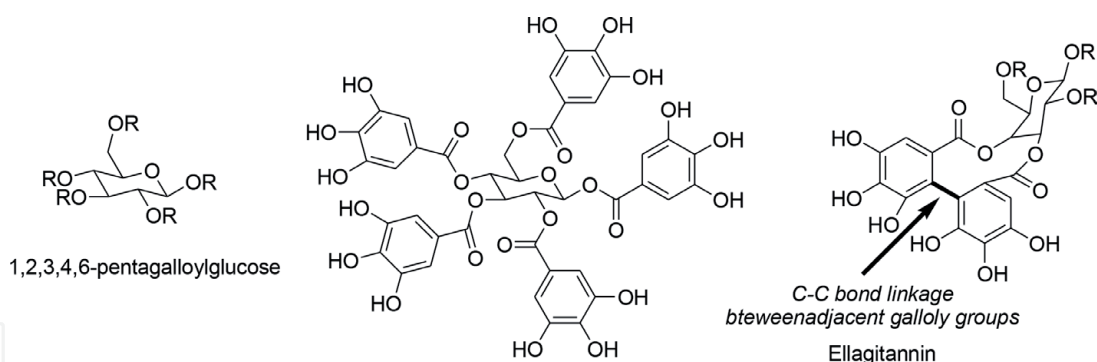
### 2.2.2 Tannins

Tannins are known to bind to and precipitate proteins and amino acids. They are subdivided into three types; hydrolyzable, condensed and complex. Hydrolyzable tannins can be gallotannins or ellagitannins. Gallotannins are polyols that are substituted with gallic acid units. The galloyl units in gallotannins are linked by depside (ester) linkages. Commonly the polyol core is a D-glucose that is substituted with gallic acid units. Tannic acid is an example of gallotannins (**Figure 16**).

Similar to gallotannins, ellagitannins are hydrolysable 1,2,3,4,6-pentagalloyl-glucose. However, unlike gallotannins characterized by depside linkages, adjacent galloyl groups in ellagitannins are linked by C-C bonds (**Figure 17**).



**Figure 16.**  
Gallotannins.



**Figure 17.**  
Structure of ellagitannin.

Condensed tannins (**Figure 18**) are polymeric phenolic compounds that consist of catechin units. When depolymerized, they give anthocyanidin. Thus condensed tannins are called proanthocyanidins.

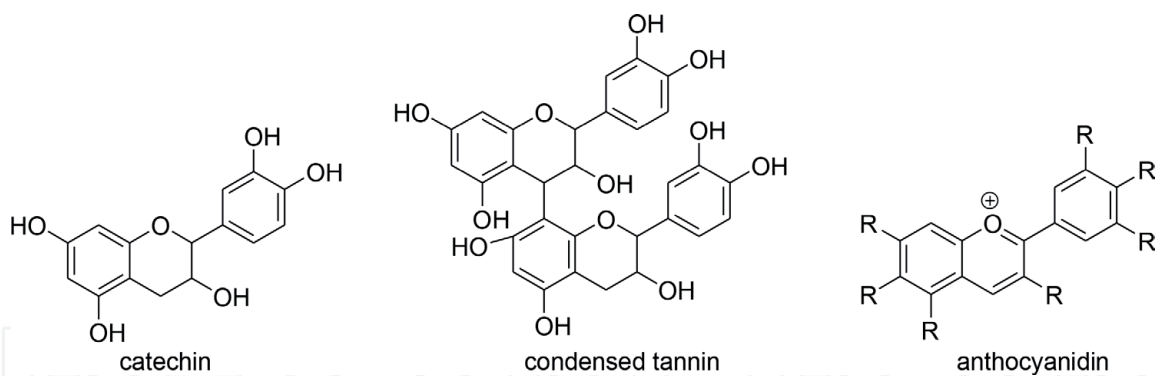
Complex tannins are gallotannins or ellagitannins bonded to a catechin unit (**Figure 19**).

## 2.3 Others phenolic compounds

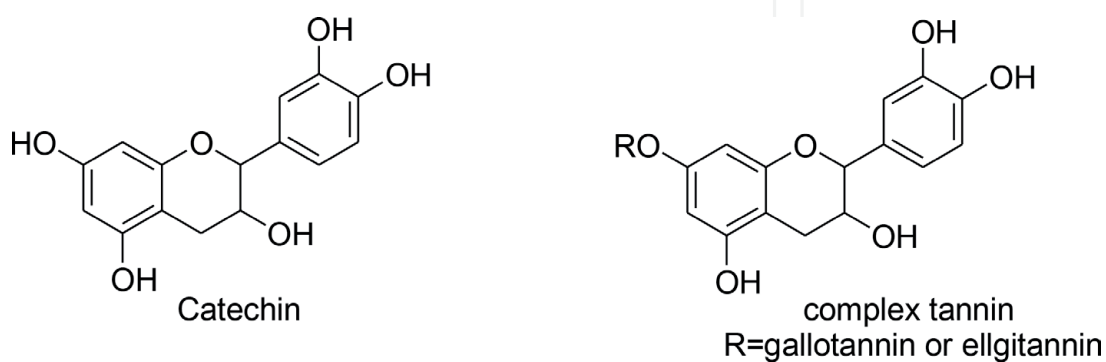
### 2.3.1 Stilbenes

Stilbenes are phenolic compounds in which two phenol units are linked by two-doubly bonded carbons (**Figure 18**). Examples of stilbenes include resveratrol, pterostilbene and piceatannol shown (**Figure 20**).

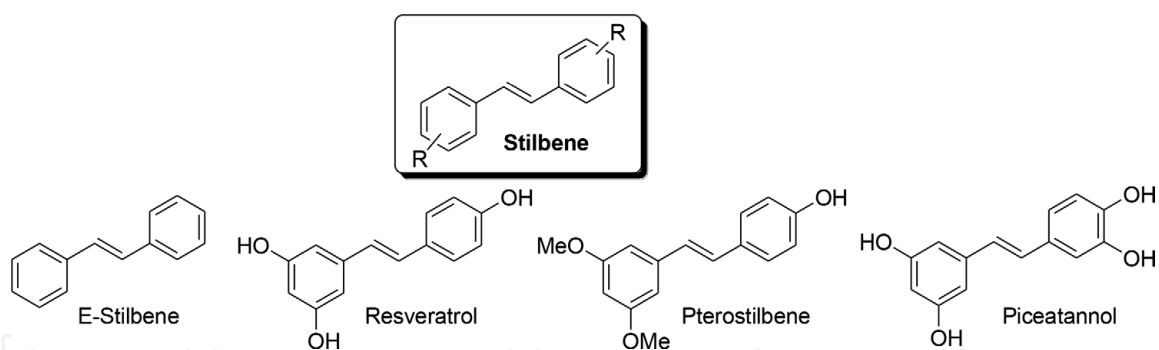




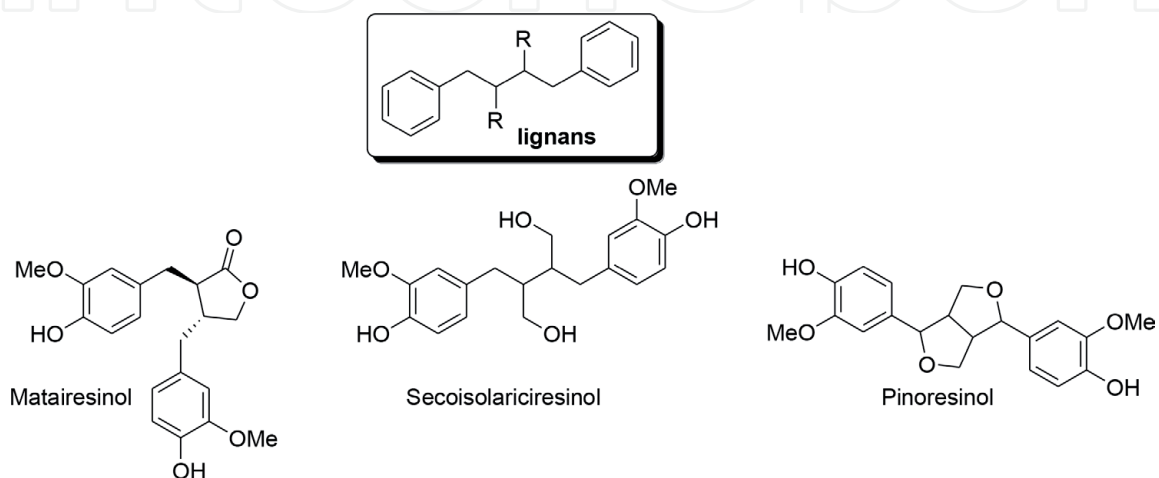
**Figure 18.**  
General structure of condensed tannins.



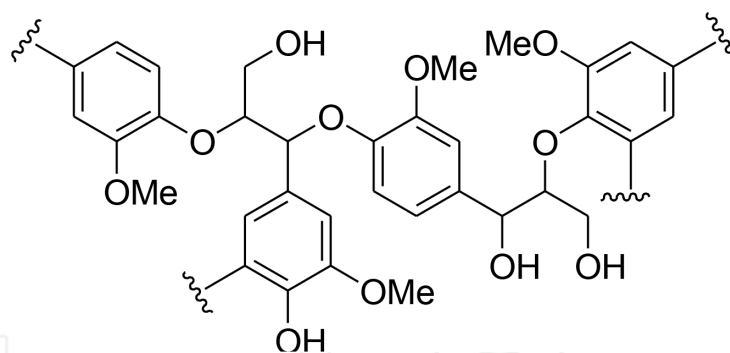
**Figure 19.**  
General structure of complex tannins.



**Figure 20.**  
Stilbenes.



**Figure 21.**  
General structure of lignans and examples.



**Figure 22.**  
A segment of lignins.

### 2.3.2 Lignans

Lignans consist of two phenol units linked by four carbons. Examples include matairesinol, secoisolariciresinol and pinoresinol (**Figure 21**).

### 2.3.3 Lignins

Lignins consist of phenol units or phenolic compounds that are linked with each other by carbon chains (**Figure 22**). Lignins are high molecular weight polymers.

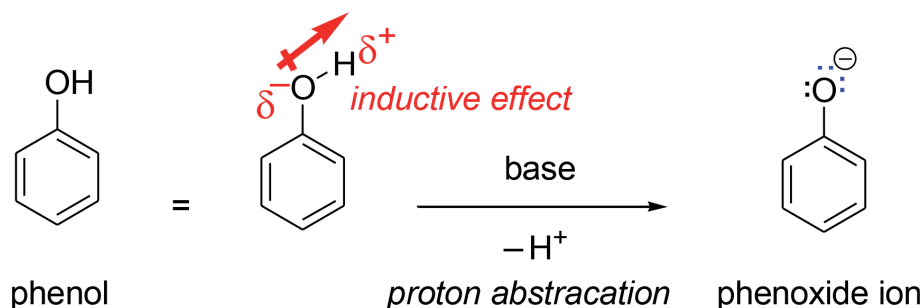
## 3. Chemistry

### 3.1 Acidity

An important chemical feature of phenolic compounds is the acidity of the phenol moiety. The unequal shift of electrons in the O-H bond in phenol is caused by the difference in electronegativity between H and O. The arbitrary electronegativity values according to Pauling scale are 2.1 and 3.5 respectively. Thus the formed inductive effect imparts a positive partial charge on the H atom (**Figure 23**). Thus the H atom is removable in the form of a proton by a suitable base. The pKa of phenol is 9.9, relatively stronger as an acid than aliphatic alcohols (pKa ca. 16). [13]

The resultant conjugate base, the phenoxide ion, is further stabilized by resonance (**Figure 24**). The lone pair placed as a result of proton abstraction is delocalized over the phenyl ring. Electron delocalization by resonance results in stabilization of the phenoxide ion.

Substituents on the phenol ring can have a significant effect on the acidity of phenol (**Figure 25**). For instance, electron withdrawing groups (EWG) increase

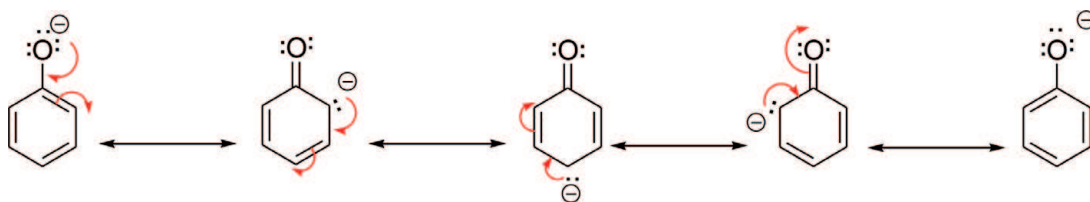


**Figure 23.**  
Acidity of phenol caused by inductive effect.

the acidity of phenol. EWG stabilize the phenoxide ion further by inductive and resonance effects. On the other hand, electron donating groups (EDG) decrease the acidity of phenol. EDG lower the stability of the phenoxide ion by donating of electrons by inductive or resonance effects.

For example, 4-nitrophenol with a pKa of around 7 is more acidic than phenol itself. The nitro group withdraws electrons by resonance and thus imparts an additional resonance stabilization of the phenoxide ion (**Figure 26**). Thus, 4-nitrophenoxide ion is more stable than the simple unsubstituted phenoxide ion.

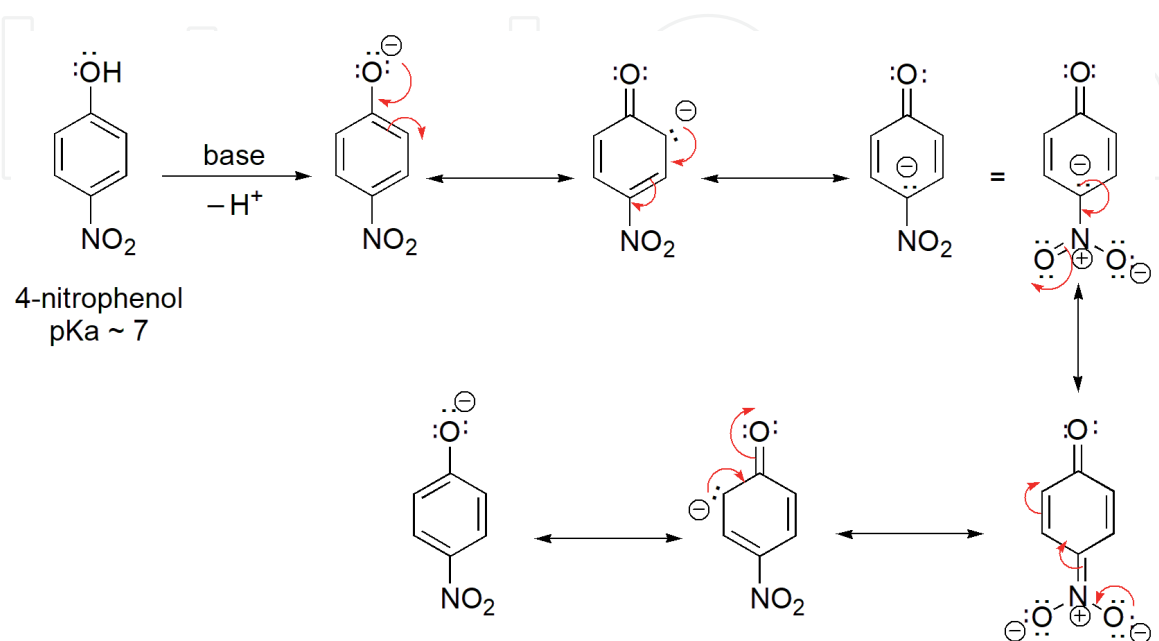
For example, 4-aminophenol with a pKa of around 10.3, is less acidic than phenol itself. The nitro group imparts an additional resonance stabilization of the phenoxide ion which is then more stable than the simple unsubstituted phenoxide ion (**Figure 27**).



**Figure 24.**  
Resonance stabilization of the conjugate base of phenol, the phenoxide ion.



**Figure 25.**  
Effects of substituents on the acidity of phenol.



**Figure 26.**  
Resonance stabilization of the conjugate base of 4-nitrophenol.

### 3.2 Hydrogen bonding

The inductive effect of the O-H bond in phenol induces a negative partial charge on O and a positive partial charge on H. Therefore, the hydrogen (H) atom can interact with heteroatoms possessing nonbonding electrons, such as O, N, F. This type of interaction is noncovalent and rather electrostatic and constitutes hydrogen-bonding (H-bonding). [14] The H atom of the O-H bond in phenol can form a H-bond with the O atom in another phenol molecule, constituting intramolecular H-bonding (Figure 28). In addition, the H atom is also capable of interacting with heteroatoms in other molecules to form intermolecular H-bonding.

Phenolic compound with adjacent hydroxyl groups such as protocatechuic acid, can exhibit intramolecular H-bonding (Figure 29). Phenolic compounds with adjacent hydroxyl and alkoxy groups are also capable of intramolecular H-bonding.

Another structural possibility for intramolecular H-bonding is the presence of a hydroxyl group *ortho* to a carbonyl group as in butein (a chalcone type) (Figure 30).

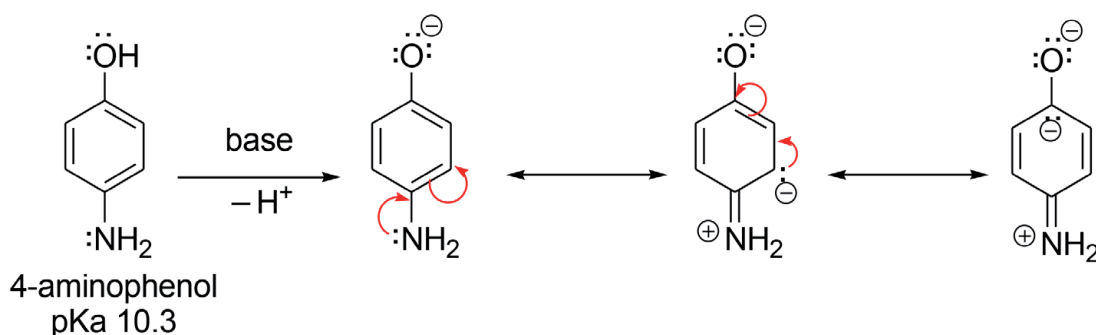


Figure 27.  
Resonance stabilization of the conjugate base of 4-aminophenol.

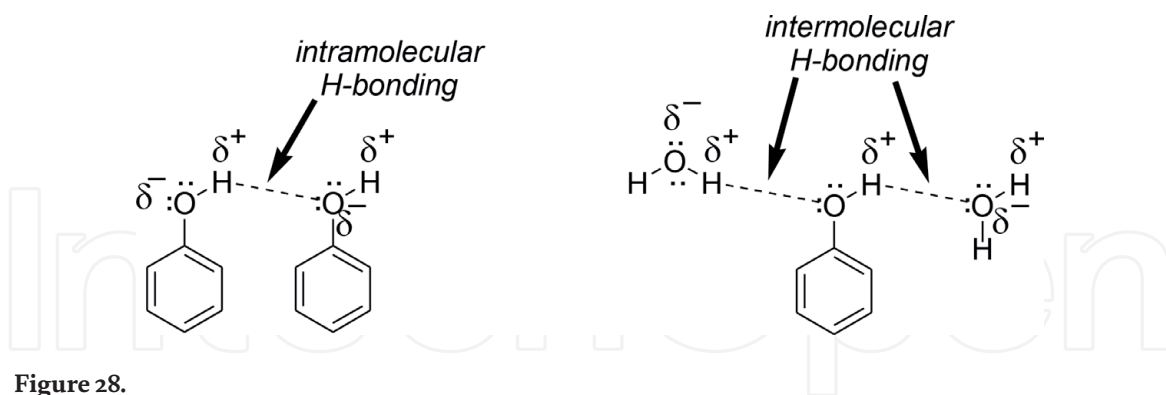


Figure 28.  
Intramolecular and intermolecular H-bonding of phenol.

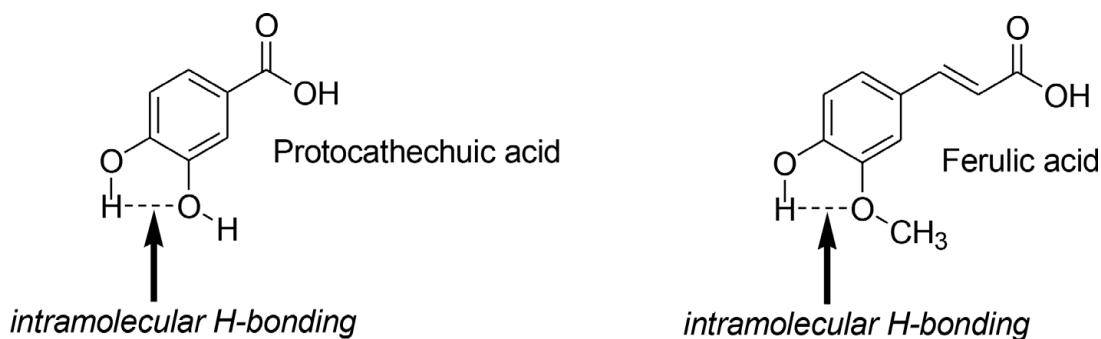


Figure 29.  
Intramolecular H-bonding of phenolic compounds.

Another structural possibility is the presence of a hydroxyl group and a carbonyl group separated by a ring junction as in flavanone.

Intramolecular H-bonding can result in formation of five-membered rings as in Ferulic acid (**Figure 29**) and six-membered rings as in Flavanone (**Figure 30**). Such rings are inherently stable which would consequently influence the chemistry of phenolic compounds. For instance, intramolecular H-bonding can lower the solubility and reactivity of phenolic compounds in esterification and etherification reactions.

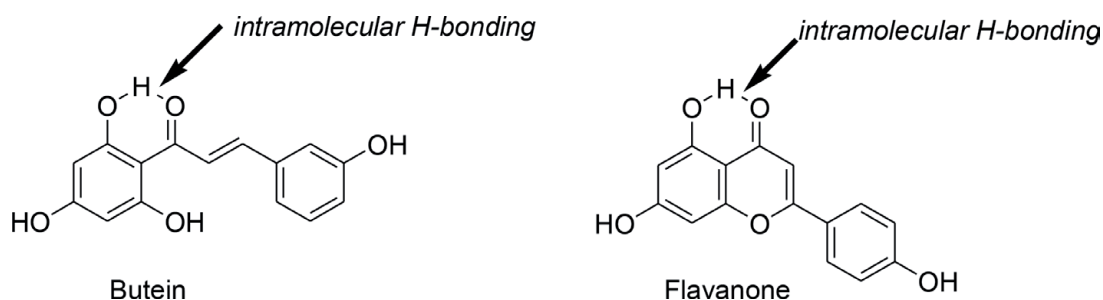
### 3.3 Esterification reactions

Phenolic compounds can take part in esterification reactions. They can contribute the phenolic hydroxyl group upon reactions with a carboxylic acid or a carboxylic acid derivative such as acid anhydrides or acid halides typified by acid chlorides (**Figure 31**), forming phenolic esters.

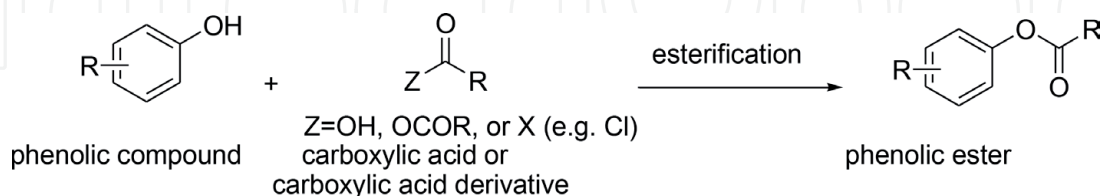
The other esterification possibility of phenolic compounds is for them to contribute their carboxyl group upon reactions with alcohols to produce the corresponding phenolic ester (**Figure 32**).

### 3.4 Etherification reactions

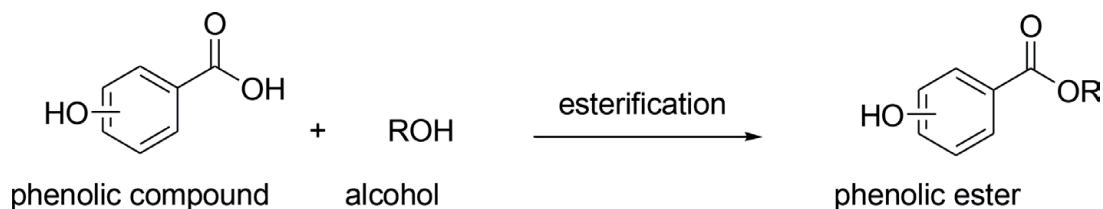
Phenolic compounds can undergo etherification reactions. Thus they can react with alcohols to produce the corresponding phenolic ether (**Figure 33**).



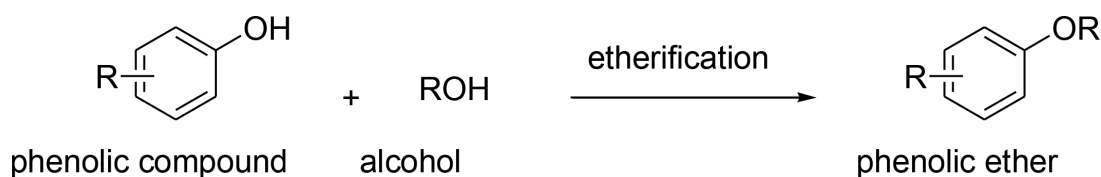
**Figure 30.**  
*Intramolecular H-bonding of phenolic compounds.*



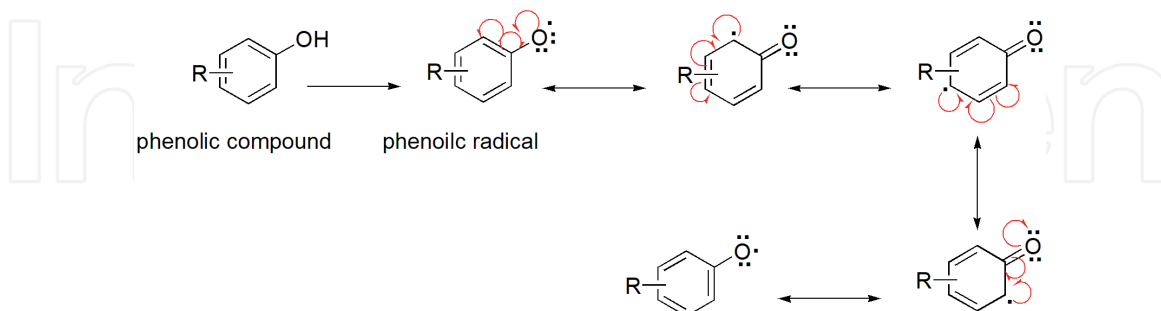
**Figure 31.**  
*Esterification of phenolic compounds.*



**Figure 32.**  
*Esterification of phenolic compounds.*



**Figure 33.**  
*Etherification of phenolic compounds.*



**Figure 34.**  
*Oxidation of phenolic compounds to form phenolic radicals.*

### 3.5 Oxidation

Phenolic compounds can undergo oxidation reactions. Homolytic (symmetrical) oxidative O-H bond cleavage gives rise to a phenolic radical (**Figure 34**). Such radicals are stabilized by resonance by delocalization of the resultant single electron over the ring.

## 4. Analysis

Phenolic compounds can be analyzed using various techniques. Mass spectrometry (MS), high performance liquid chromatography (HPLC), gas chromatography (GC), GC-MS, calorimetry, ultraviolet (UV), ultraviolet-visible (UV/VIS) spectrophotometry, and other spectrophotometric techniques represent examples of such techniques. [15–18] Total phenolic content (TPC) of phenolic compounds in plants is commonly measured using spectrophotometry techniques such as Folin-Denis and Folin-Ciocalteu methods. [19] The latter method which is based on electron-transfer, was found to be more preferable and thus more common. [15, 16]. GC has been used to analyze phenolic acids, condensed tannins, flavones, and flavonoids. HPLC has been used to analyze anthocyanins, hydrolysable tannins, phenolic acids, cinnamic acids and flavonoids. [18] Anthocyanins have been analyzed using UV absorption at a wavelength range of 489–550 nm. [18] Hydrolysable tannins have been also analyzed at a wavelength of 500–550 nm. [18]. Based on their ability to bind proteins, tannins have been analyzed using protein-binding methods. [20, 21] Calorimetric methods have been used to determine the TPC in flavonoids and tannins. Other techniques for analysis of phenolic compounds include capillary electrophoresis (CE) and micellar electro-kinetic chromatography. [22]

Recent methods of analysis include ultra-high performance liquid chromatography (UHPLC) [23], ultra-high performance liquid chromatography-quadrupole-orbitrap (UHPLC-Q-Orbitrap) [24], high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) [25], liquid chromatography coupled with electrospray-ionization triple quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF-MS) and high-performance liquid chromatography-photo diode array (HPLC-PDA) [26], ESI-MS/MS [27].

## 5. Synthesis

### 5.1 Biosynthesis

There are two general routes for the biosynthesis of phenolic compounds; shikimic acid pathway and the acetic acid pathway. [12, 28] In the shikimic acid pathway (**Figure 35**), phosphoenolpyruvate and erythrose-4-phosphate react in few steps to provide 3-dehydroquinate. Dehydration with shikimate dehydrogenase gives 3-dehydroshikimic acid. Reduction with NADPH gives shikimic acid. 3-Dehydroshikimic acid could lead to gallic acid in several steps. Shikimic acid is then converted into chorismic acid which undergoes Claisen rearrangement to afford prephenic acid. The product is then converted in several steps into tyrosine. The amino acid serves as a central point and a crucial precursor for the biosynthesis of various phenolic compounds (**Figure 35**).

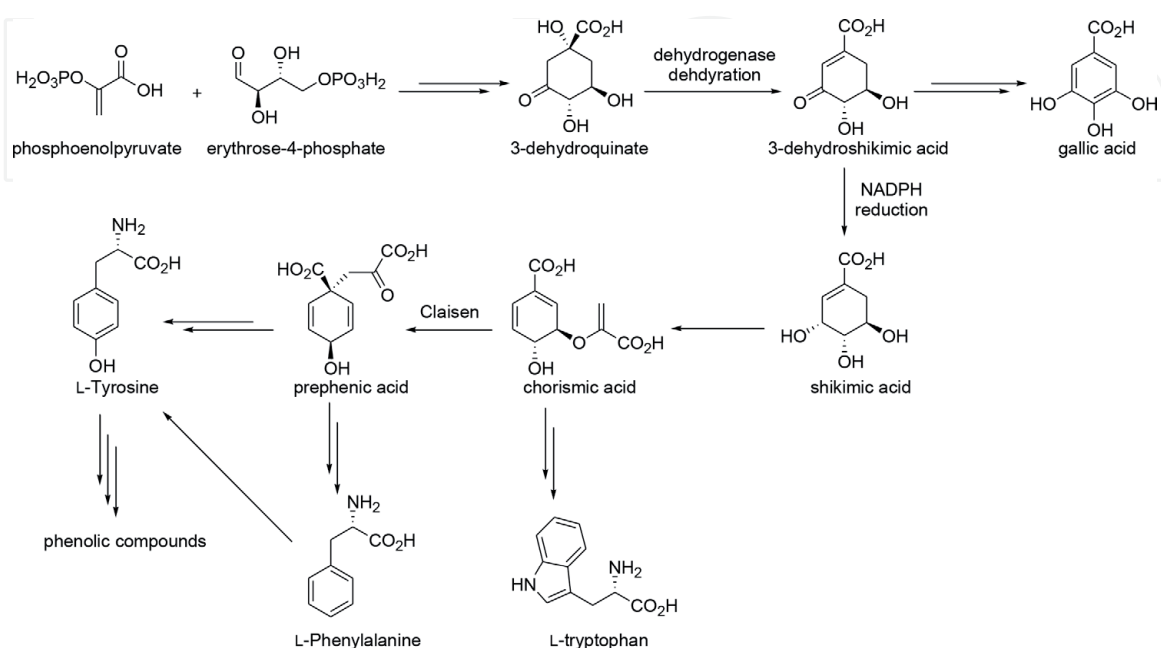
Another route toward phenolic compounds, is the phenylpropanoid pathway (**Figure 36**). This route is essentially similar to the shikimic acid pathway until L-phenylalanine stage where the phenylpropanoid pathway takes form. L-Phenylalanine undergoes deamination catalyzed by phenylalanine ammonia lyase (PAL) enzyme to give cinnamic acid. Hydroxylation followed by conversion to the Coenzyme A provides *p*-coumaroyl Coenzyme A. This molecule serves as a central point toward various phenolic compounds.

### 5.2 Synthesis

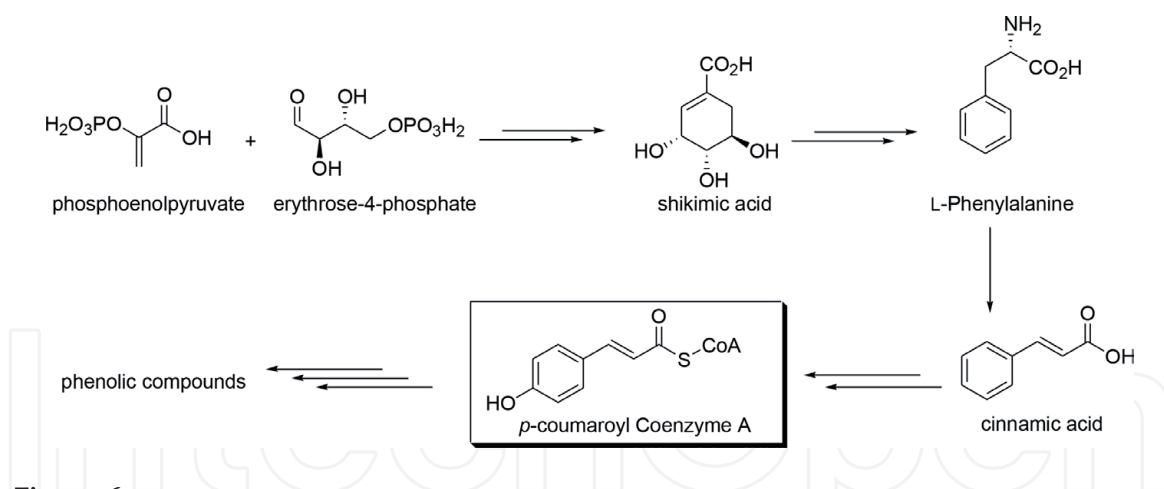
There have been many methods that are used to synthesize phenolic compounds in the laboratory. For instance, phenolic compounds were obtained using Copper-catalyzed synthesis from 1,3-dicarbonyl compounds employing dimethylsulfoxide (DMSO) as a methylene source (**Figure 37**). [29]

Phenolic compounds have also been obtained using biocatalysis. Thus phenolic compounds were synthesized by lipase-catalyzed synthesis (**Figure 38**). [30]

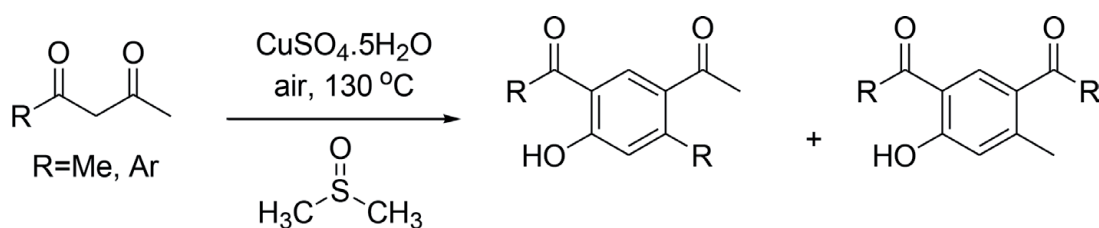
Various imine phenolic compounds were synthesized starting from 3-aminobenzoic acids as schematically represented below (**Figure 39**). [31]



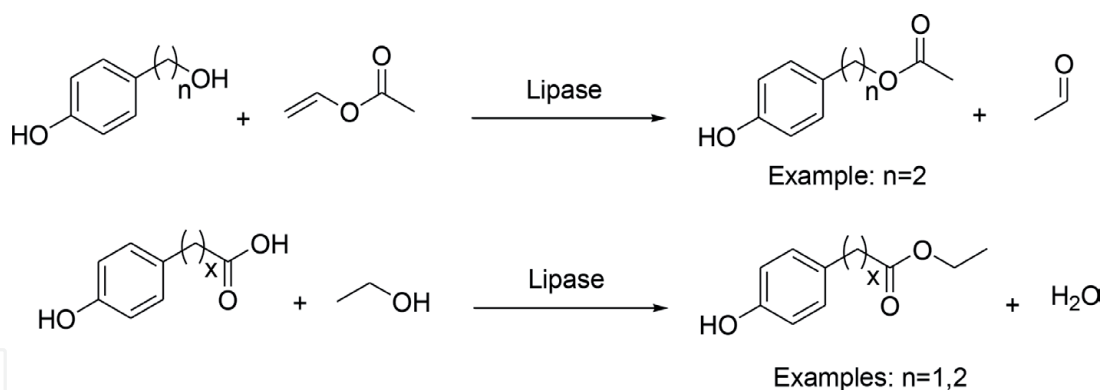
**Figure 35.** Shikimic acid pathway toward phenolic compounds.



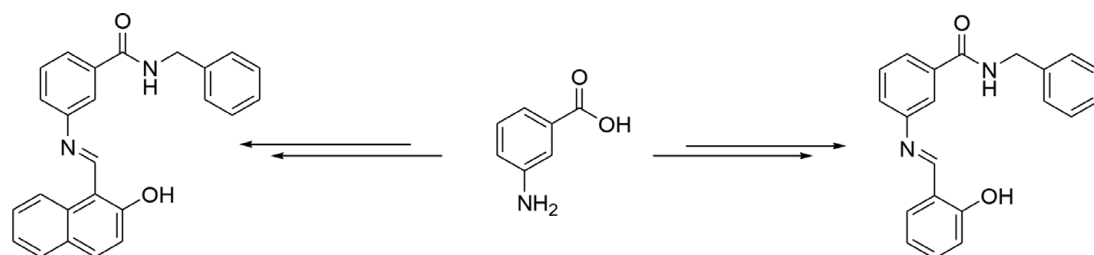
**Figure 36.**  
 The phenylpropanoid pathway toward phenolic compounds.



**Figure 37.**  
 Copper-catalyzed synthesis of phenolic compounds from 1,3-dicarbonyl compounds.



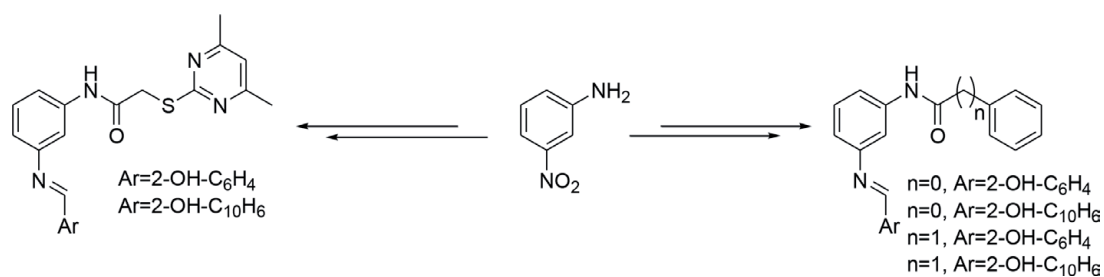
**Figure 38.**  
 Lipase-catalyzed synthesis of phenolic compounds.



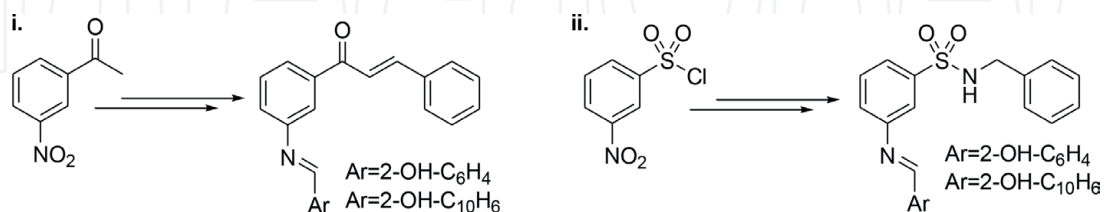
**Figure 39.**  
 Synthesis of imine phenolic compounds.

Various Schiff bases were also accessed from 3-nitroaniline (**Figure 40**). [31]  
 Other azomethine-based phenolic compounds were prepared from 3-nitroacetophenone (**Figure 41 i**). [31]

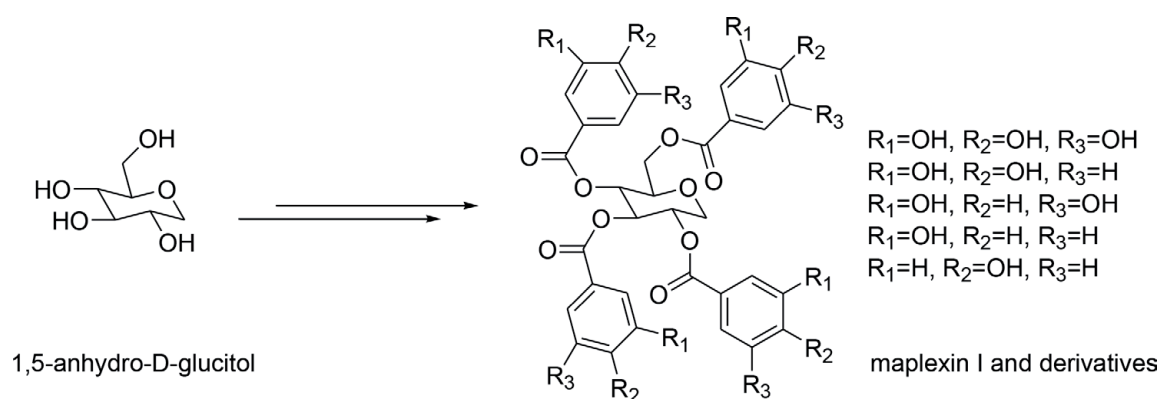




**Figure 40.**  
Synthesis of imine phenolic compounds.



**Figure 41.**  
Synthesis of imine phenolic compounds.



**Figure 42.**  
Synthesis of maplexin J and its derivatives from 1,5-anhydro-D-glucitol.

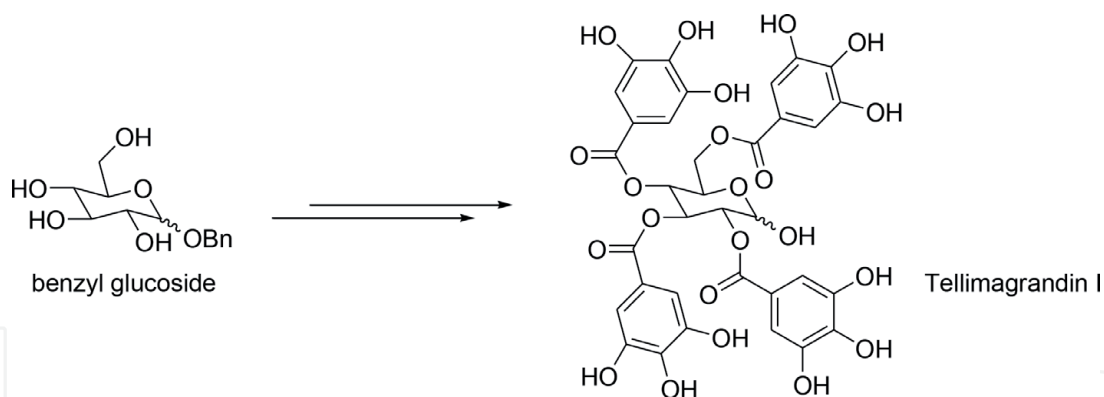
Sulfonyl amide phenolic compounds were prepared from 3-nitrobenzenesulfonyl chloride (**Figure 41 ii**). [31]

Carbohydrate-based polyphenolic compounds were synthesized from 1,5-anhydro-D-glucitol as schematically shown below (**Figure 42**). [32] Thus maplexin J ( $R_1 = R_2 = R_3 = OH$ ) and its derivatives were synthesized using this route.

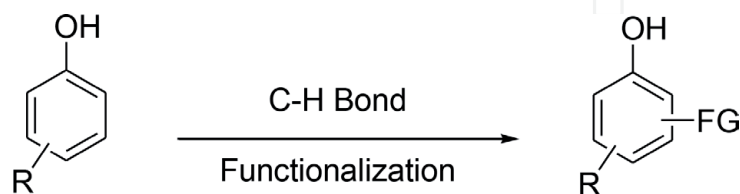
Another example is the synthesis of an analog of tellimagrandin I from benzyl glucoside (**Figure 43**). [32]

Functionalization and expeditious transformation of phenol derivatives into new functional molecules have been made possible with metal-catalyzed C-H bond functionalization. [28, 29] The C-H activation science has allowed accessing new and further functionalized phenol derivatives in an expedient and efficient manner (**Figure 44**). Thus catalysts based on various transition metals such as Pd, Rh, Ru, Ir, Au and Fe have allowed functionalization of inert C-H bonds in simple phenolic compounds and subsequently their transformation into new functionalized molecules. [33, 34]

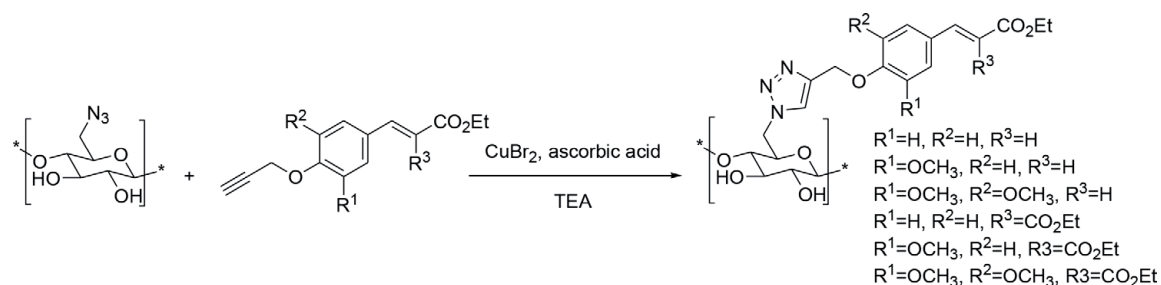
Recently, 1,3-dipolar cycloaddition (Click chemistry) of cellulose-based azides with alkynes derived from phenolic compounds were transformed into new



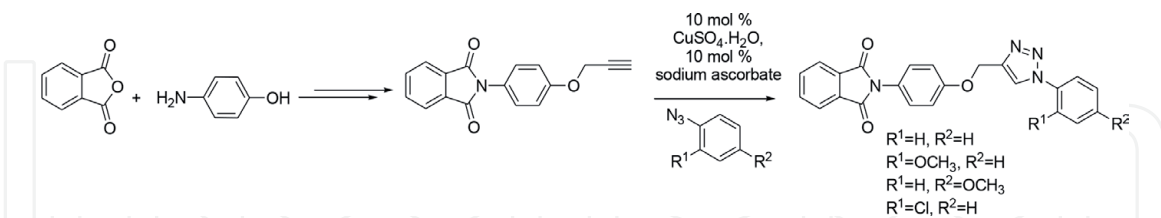
**Figure 43.**  
 Synthesis of tellimagrandin I analog.



**Figure 44.**  
 C-H bond functionalization of phenol derivatives.



**Figure 45.**  
 1,3-Dipolar cycloaddition of cellulose-based azides with alkyne-phenolic compounds.

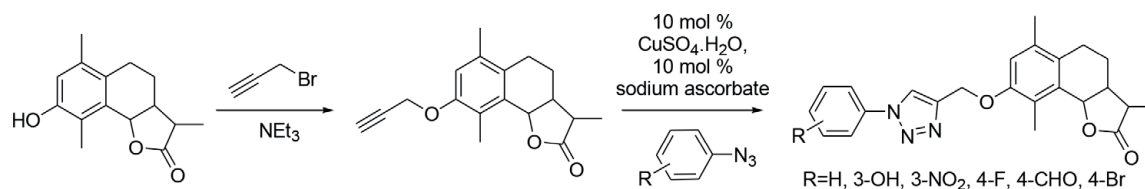


**Figure 46.**  
 1,3-Dipolar cycloaddition of alkyne-phenolic compounds with aryl azides.

phenolic compounds-based adducts (**Figure 45**). The new triazole products display some applicable anti UV properties. [35].

Simple phenolic compounds such as 4-aminophenol were transformed, *via* Click chemistry between their alkyne and aryl azides, into new triazole-containing isoindoline derivatives (**Figure 46**). The products obtained were of potential biological activities. [36]

Natural phenolic compounds were transformed via their alkyne-derivatives into the corresponding triazole adducts by the click reaction with aryl azides (**Figure 47**). The method demonstrates an example of synthetic elaboration of phenolic compounds into new ones of potential biological functions. [37].



**Figure 47.**  
1,3-Diploar cycloaddition of alkynes derived from natural phenolic compounds and aryl azides.

## 6. Future perspective and industrial applications

Phenolic compounds possess a wide range of biological activities such as antioxidant, anti-inflammatory, and antimicrobial properties. Such properties allow phenolic compounds be able to reduce various illnesses and diseases such as cardiovascular diseases, diabetes, cancer, and hypertension. Therefore, they can be used in pharmaceutical industry as therapeutic agents. The antioxidant and antimicrobial properties enable phenolic compounds to function as food preservatives and additives. Thus they have also applications in food industry. In addition, phenolic compounds have applications in cosmetic and packaging industries. Exploitation of the full potential of phenolic compounds lies in the development of prudent and efficient methods for their detection, isolation, and analysis. Also, a key direction is their synthetic transformation and elaboration into new and potentially more biologically active molecules. Moreover, another prospect is the developments of new methods for the expeditious synthesis of phenolic compounds.

## 7. Conclusions


Phenolic compounds are ubiquitous in nature. Phenolic compounds display a wide range of biological activities such as antioxidant, antimicrobial and anti-inflammatory properties. Therefore, they have versatile applications in various industries such as pharmaceutical and food industries. Developments of efficient methods and protocols for the identification of phenolic compounds, their detection and analysis should continue. Due to their high potential and applications in various industries, development of efficient methods for their synthesis and synthetic elaborations into new phenolic compounds is sought. This chapter has been an attempt to provide the reader with a quick guide and reference for the classification, chemistry, analysis and synthesis of phenolic compounds.

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