Natural Phenols

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Contributor: Federica Sabuzi

Phenols are widespread in nature, being the major components of several plants and essential oils. Natural phenols' anti-microbial, anti-bacterial, anti-oxidant, pharmacological and nutritional properties are, nowadays, well established. Hence, given their peculiar biological role, numerous studies are currently ongoing to overcome their limitations, as well as to enhance their activity.

carvacrol thymol eugenol resveratrol hispolon hydroxytyrosol lipidic phenols phenolic acids polyphenols curcumin

1. Introduction

Natural phenols, mainly of vegetable origin, are receiving increasing attention, as insight into their biological activity increases.

In recent years, many reviews appeared about phenolic profiles of plants and/or essential oils, evidencing anti-microbial, anti-bacterial [1][2][3][4], antioxidant [5][6][7][8][9][10], as well as pharmacological [11][12][13][14][15][16][17][18] and nutritional [19][20][21] properties, together with a very informing book [22]. In view of their importance, studies were aimed at breeding plants able to increase the content of bioactive phenols [23]. The research in the field continues, and more and more plants are investigated for their phenolic content and related bioactivity [24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41]. The antioxidant activity of natural phenols has been related to their scavenger ability towards free radicals [42]. Particularly interesting is the possibility to encapsulate phenols—as well as other natural compounds—in chitosan biopolymers [43], or in β-cyclodextrin [44].

It must be noticed that the application of modern extractive techniques [45][46][47][48][49][50][51][52] makes the determination of phenolic compounds in plant matrices more accessible and complete.

New applications of natural phenols in different fields are reported in fish aquaculture [53], sport performances [54], fish gelatin and gelatin from bovine skin modification by cross-linking with natural phenolic acids [55][56]. Advanced extraction technologies allowed the use of phenolic extracts from some plants for food preservation [57][58][59][60]. Moreover, technological applications are becoming available, such as anti-bacterial films based on cellulose/phenolic species [61], antimicrobials packaging films based on nano-encapsulation of bioactive oils through emulsion polymerization [62], fire-resistant phenolic foams [63] and natural fiber-reinforced composites with lignin phenol binder [64].

Additionally, it is worth signaling the use of natural phenolic compounds as building blocks to obtain functional materials [65] or as antioxidants for biodiesel [66].

With so much information collected and available, the next step was the effort to understand the structural factors responsible for bioactivity, examining the structure–activity relationship of antioxidant phenolic compounds [67][68].

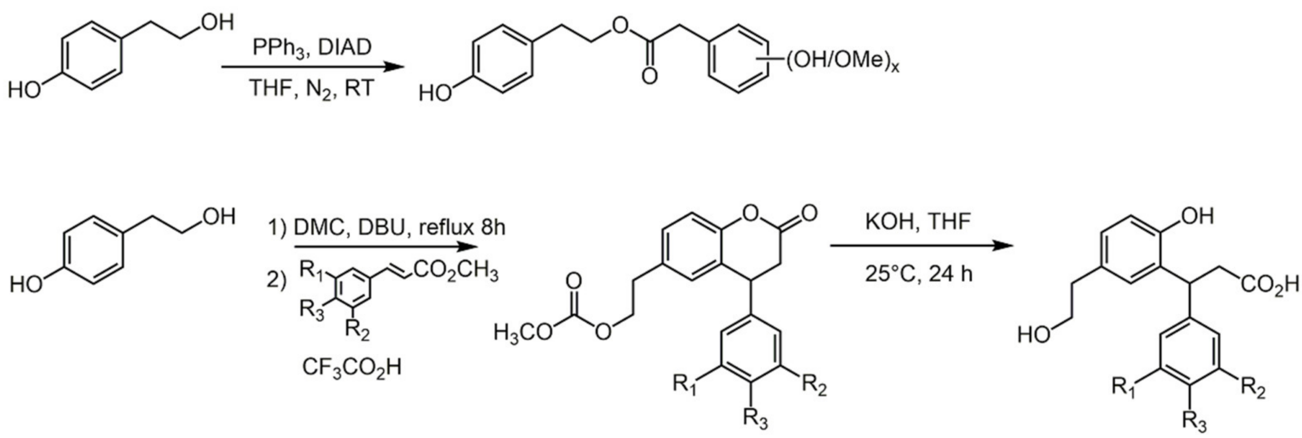
From the chemical point of view, it may be interesting to look for chemical derivatization of natural phenols leading to eventually enhanced biological activity. As a matter of fact, treatment with diazomethane of phenolic extracts led to derivatives more suitable as antioxidants for lipophilic foods [69]. Considering the importance for human health, representative methods to chemically modify the natural phenols were discussed [70], as well as reviews of enzymatic modification [71] and of metabolic engineering for microbial biosynthesis of natural compounds, among which phenols, were reported [72].

2. Tailored Functionalization of Natural Phenols to Improve Biological Activity

2.1. Monophenols

Monophenol functionalization is attracting the interest of a growing number of researchers, since the synthesis of new biologically active derivatives starting from natural compounds is a proficient tool to improve their properties. In fact, tailored functionalization is a valuable strategy to overcome natural phenol weaknesses such as toxicity, low water solubility, as well as to mild their strong fragrances, that often limit their application [73][74][75][76][77][78]. Carvacrol, thymol and eugenol are amongst the most widespread phenols in nature, usually responsible for beneficial plant properties.

As an example, the antioxidant activity of tyrosol (2-(4-hydroxyphenyl)-ethanol), which is an abundant phenol in olive oil, responsible for oil beneficial properties [79], can be sensibly enhanced through esterification of the alcoholic hydroxyl group with different phenolic acids (Scheme 1) [80]. Analogously, hydroarylation with cinnamic esters improves the antioxidant properties of tyrosol, especially in the presence of additional hydroxyl group in the aromatic ring of the acidic moiety (Scheme 1) [81].



Scheme 1. Tyrosol esterification with phenolic acids (top) [80]; tyrosol hydroarylation with cinnamic esters (bottom) [81]. Abbreviations: DIAD = diisopropyl azodicarboxylate; DMC = dimethyl carbonate; DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.

Carvacrol (5-isopropyl-2-methylphenol) is a phenolic monoterpenoid compound, and it is a major component of oregano and thyme essential oils. Together with its isomer, thymol (2-isopropyl-5-methylphenol), it is the main active ingredient responsible for essential oils' biological activity [82][83][84]. In fact, carvacrol's peculiar antibacterial, antifungal, anti-inflammatory, anxiolytic and anticancer activities are currently well established, and the FDA (Food and Drug Administration) has approved its use as an additive in food products. Nonetheless, the research of new carvacrol analogues is currently inspiring several research groups, with the aim to extend the potential application of the compound [85]. Carvacrol functionalization usually occurs at the -OH moiety; indeed, a wide variety of synthetic carvacryl esters can be found in the literature. Obviously, through phenol esterification, variegated functionalized products can be accessed [86], to be explored in several areas.

Next to carvacrol, its isomer, thymol, is widely used as an antibacterial, antifungal, antioxidant and anti-inflammatory active ingredient in several products, as well as a food preservative [84][87]. Indeed, several natural and synthetic thymol derivatives have been proposed over the years to further broaden its application at the industrial level [88][89][90]. Quite a few thymol derivatives have been synthesized and evaluated for different biological purposes [86][91][92][93][94]. Thymol functionalization through esterification or etherification reactions constitutes one of the most useful approaches to access a wide library of different bio-active molecules. Thymol esterification usually occurs in the classical conditions, reacting thymol with the appropriate anhydride or acyl chloride in the presence of a base. MW-assisted procedures in aqueous medium have also been proposed, to perform reactions in reduced times and with improved yields [95]. Different studies also demonstrated that halogenation is a proficient strategy to enhance thymol biological activity [96][97][98][99][100][101].

Eugenol (4-allyl-2-methoxyphenol) is the major component of clove essential oils, but it can be also found in minor amounts in cinnamon, clover pepper and other plants. It is used in perfumeries for its pleasant fragrance, as a flavoring agent in foods, as antiseptic and disinfectant in dental products and in many other fields [102]. Eugenol can be readily functionalized through the chemical transformation of the phenolic -OH group (mainly via the classical etherification and esterification reactions) [103][104][105][106][107][108][109], on the aromatic ring (through nitration reaction or Mannich bases formation) [110][111][112], as well as on the allylic functionality, through epoxidation [108].

2.2. Diphenols

Natural diphenols, including catechol, resorcinol and hydroquinone derivatives, are widespread in nature, being commonly found in several vegetables and fruits. Such natural compounds are usually characterized by peculiar anti-oxidant and anti-inflammatory activity. Some of them have immunomodulatory and anticancer active ingredients. Therefore, natural diphenols are often used as scaffolds to prepare new efficient biologically active drugs. Although there is a widespread presence of bioactive diphenols in nature, the attention is dedicated to the tailored functionalization of resveratrol, hispolon and hydroxytyrosol, which constitute abundant and highly active natural phenolic compounds (**Figure 1**).[113][114][115]

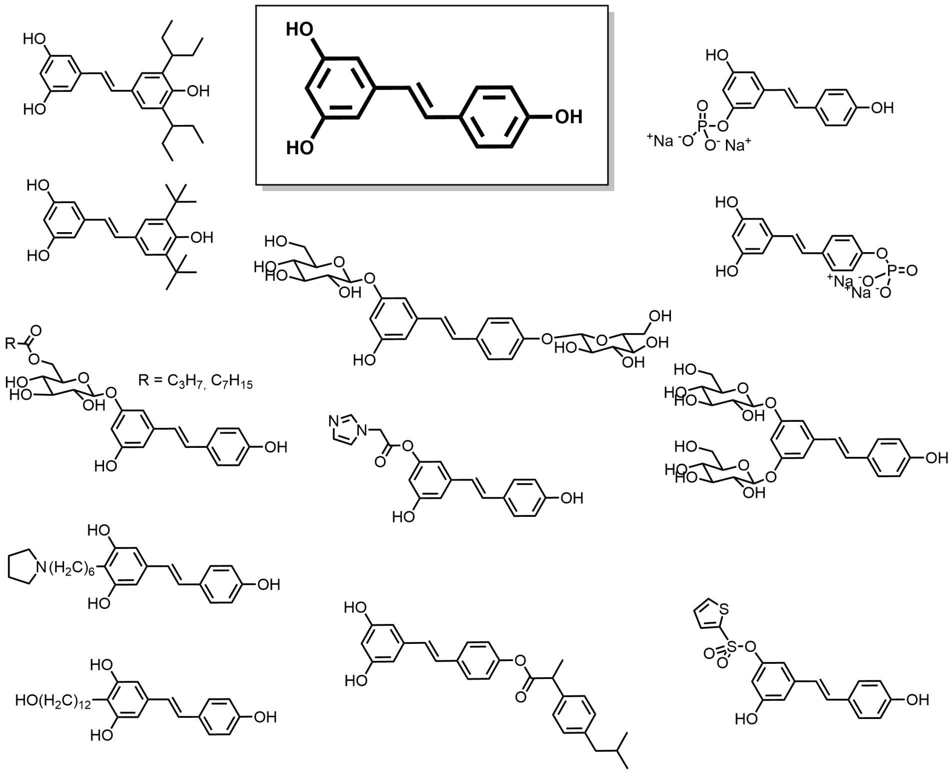


Figure 1. Structure of selected resveratrol derivatives.

2.3. Phenolic Acids

Phenolic acids are hydroxy or methoxy derivatives of benzoic acid or of cinnamic acid (3-phenylpropenoic acid). They are diffused in many plants (for example, they are among the most abundant natural antioxidants of virgin olive oil [116]). The more frequent phenolic acids are summarized in **Figure 2**.

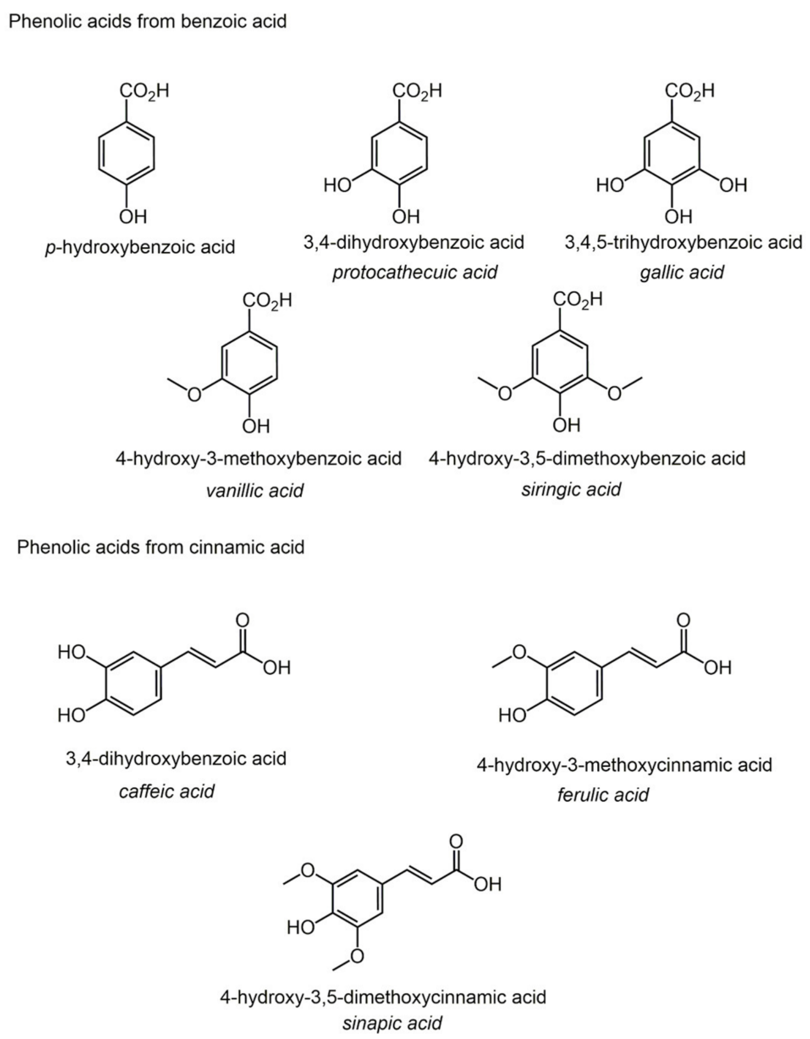


Figure 2. Bioactive phenolic acids widespread in plants.

Occurrence, biological and pharmacological functions of monocyclic phenolic acids were reviewed, evidencing their wide distribution and variety of functions [117][118][119], together with their promising therapeutic applications [120][121][122][123][124]. As an example, development of gallic acid derivatives as pharmacological agents [125][126] was recently discussed. Similarly, features and potential application of ferulic acid derivatives [127][128][129][130][131] and natural and synthetic products derived from caffeic acid [132] were reviewed.

Therefore, the appealing properties of phenolic acid derivatives are unambiguously affirmed.

2.4. Lipidic Phenols

Lipidic phenols (or phenolic lipids, also called phenolipids) are phenols substituted with lipophilic chains, that confer to the molecule amphiphilic characteristics. An important phenolic lipid is *α*-tocoferol [133].

The importance of natural lipidic phenols has been underestimated for a long time [134]. However, their excellent antioxidant, antigenotoxic and cytostatic properties are now established [135], together with their bioactivity in influencing biological pathways involved in the Alzheimer's disease pathogenesis [136]. Anti-inflammatory and anti-arthritis activities were also reported for lipidic phenols extracted from cashew nut (*Anacardium occidentale*) [137].

Because of the importance of such class of compounds, several synthetic lipidic phenols have been proposed in recent decades to further extend their biological applications.

2.5. Polyphenols

Natural polyphenols constitute a numerous and largely distributed group of bioactive molecules in edible plants, with bioactivities ranging from cardiovascular protection to prevention of cancer [138][139][140][141].

Polyphenols are characterized by the presence of benzo-fused heteroaromatic ring of the pyrane or pyrilium type. They are usually named by a semi-systematic nomenclature, based on the parent heterocycle. Thus, benzopyrane derivatives with a phenyl substituent are named flavanes, while phenyl substituted benzopyranones are indicated as flavones. The structures of parent compounds and their phenyl derivatives are collected in **Figure 3**.

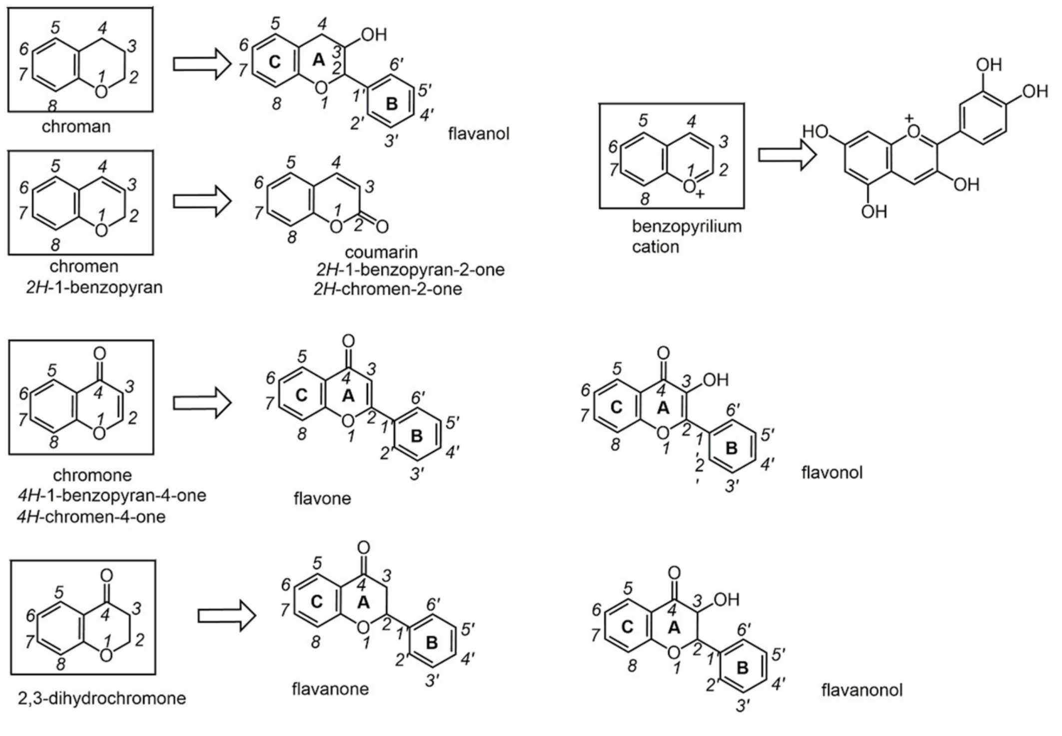


Figure 3. Structures of parent heterocyclic compounds and their phenyl derivatives present in polyphenols.

The synthesis of natural and semi-synthetic highly oxidized bioactive polyphenols was reviewed in 2008, discussing advances and challenges [142]. Alternatively, more efficient and sustainable production may come from microbial cell factories, as reviewed in 2018 [143].
Chemical transformations of natural phenols might lead to more effective species, if structural features at the basis of biological activity are understood.

2.6. Curcumin and Curcuminoids

Curcumin, [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], a yellow pigment isolated from turmeric (*Curcuma longa Linn*), is a multifunctional compound that, at least from reading the literature of the past twenty years, seems a sort of panacea for all the illness of modern society, cancer and Alzheimer's disease included. Phenolic –OH groups ensure the anti-oxidant properties, whereas the extensive conjugation due to the keto-enol equilibrium is the basis of photodynamic activity. Several recent reviews discuss the aspects of biological activity [144][145][146] and possible medical applications [147][148][149][150][151][152] of curcumins and derivatives. An increasing interest is devoted to curcumin-based drugs against neurodegenerative diseases [153], especially Alzheimer's [154] and cancer [155].

The quest for new curcumin derivatives is motivated by (i) the necessity of increasing the material availability, and (ii) the necessity of meliorating the solubility in aqueous solution.

3. Conclusions

Natural phenols and their derivatives with biological activities constitute a fast-growing research topic, in view of their many present and future applications. Their structural diversity offers many possibilities of chemical transformations, aimed at overcoming the drawbacks of natural phenols. However, apart from some guidelines that emerged from the huge number of publications, such as the need to meliorate stability and bioavailability of the bioactive compounds, the picture of structural requirements is not yet complete, in view of optimizing in vivo and in-field applications.

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