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REVIEW

Biological activity of phenolic lipids

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Abstract Phenolic lipids are a very diversified group of compounds derived from mono and dihydroxyphenols, i.e., phenol, catechol, resorcinol, and hydroquinone. Due to their strong amphiphilic character, these compounds can incorporate into erythrocytes and liposomal membranes. In this review, the antioxidant, antigenotoxic, and cytostatic activities of resorcinolic and other phenolic lipids are described. The ability of these compounds to inhibit bacterial, fungal, protozoan and parasite growth seems to depend on their interaction with proteins and/or on their membrane-disturbing properties.

Keywords Amphiphiles · Anacardic acids · Cashew nut shell liquid (CNSL) · Membrane-perturbing properties · Phenolic lipids · Resorcinolic lipids

Introduction

Phenolic lipids are secondary metabolites (not essential for cell growth) synthesized mainly by plants as well as animals, fungi, and bacteria, both during normal development and in response to stress conditions such as infection, wounds, and UV radiation. These compounds are a very diversified group and include both simple single-ring phenols and their derivatives (Table 1). Chemically, compounds called phenolic lipids are derivatives of mono- and dihydroxyphenols, namely catechol, resorcinol, and hydroquinone. The interdisciplinary interest in phenolic lipids, from pure and industrial chemistry to agricultural, nutritional, and biomedical sciences, has led an increasing of number of research groups to study different aspects of phenolic lipids activity. During the last few years, there have been several interesting and comprehensive reviews on phenolic lipids, especially resorcinolic lipids, which seem to be the most investigated compounds of this group. These started with a review by Kozubek and Tyman [1] which provided a complete description of the then known occurrence, isolation, analysis, and method of structural determination as well as the synthesis and biological activity of resorcinolic lipids. This was followed by reviews on extraction methods, chromatographic analysis, and the metabolism of alkylresorcinols [2, 3], papers on some of the properties of whole-grain cereal compounds, including resorcinolic lipids [4, 5], and reviews on secondary plant metabolites and their analysis and applications [6, 7]. Correia et al. [8] described the presence, distribution, and biological activities of different phenolic lipids of the family Anacardiaceae. The nomenclature, occurrence, chemical structures, biosynthesis and chemical synthesis, isolation and separation, as well as chemical and biological properties of anacardic acids were presented by Tyman [9], while Lubi and Thachil [10] described some industrial applications of phenolic lipids from the Anacardiaceae.

This review focuses mostly on recent data on the biological activities of phenolic lipids as antioxidant, antigenotoxic, and cytostatic agents. We also describe the ability of these compounds to inhibit bacterial, fungal, protozoan, and parasite growth, which may depend on the interaction of phenolic lipids with proteins and/or on their membrane-disturbing properties. The data presented and discussed in this review were chosen to illustrate the

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Table 1 Names of some phenolic lipids and their derivatives

Common	Chemical
Anacardic acid	6[8′(Z)-pentadecyl]salicylic acid[a]
Cardanol (alkylphenol)	3-*n*-pentadecylphenol[a]
Cardol	1,3-dihydroxy-5-*n*-pentadecylbenzene[a]
Climacostol	5-(Z)-non-2-enyl-benzene-1,3-diol
Gingkolic acid	6-[(*Z*)-10-heptadecenyl]-2-hydroxybenzoic acid
Hexyresorcinol	1,3-dihydroxy-5-heksylbenzene
Merulinic acid	Heptadec-8-enylresorcinolic acid
Methylcardol	1,3-dihydroxy-2-methyl-5-*n*-pentadecylbenzene[a]
Olivetol	1,3-dihydroxy-5-pentylbenzene
Orcinol	1,3-dihydroxy-5-methylbenzene
Panosialins	
A	5-alkyl-1,3-dihydroxybenzene-1,3-disulfates
B	5-alkyl-1,3-dihydroxybenzene-mono-sulfates
C	5-alkyl-1,3-dihydroxybenzene
6-shogaol	(E)-1-(4-hydroxy-3-methoxy-phenyl)dec-4-en-3-one
Urushiol	6-alk(en)yl-1,2-dihydroxybenzene

[a] The long aliphatic side-chain being saturated, mono-olefinic (8), diolefinic (8, 11), and tri-olefinic (8, 11, 14)

complexity of the problem. Although all reference data were collected with a great deal of effort and care, some data will nevertheless have been missed, for which the authors apologize.

Amphiphilic properties of phenolic lipids

The study of the amphiphilic properties of phenolic lipids has received much attention due to their great importance from both the practical and theoretical points of view. The presence of separate hydrophilic (hydroxy or dihydroxybenzene ring) and hydrophobic regions in phenolic lipid molecules indicates their potentially strong amphiphilic character (the representative structures of several described compounds are presented in Fig. 1). Some phenolic lipids are very useful compounds in chemical semisynthesis or other industrial applications. The study of their micellization in solution is important because in many interfacial processes the performance of the surfactant depends on its concentration and orientation at the interface. On the other hand, it was demonstrated that alkylresorcinols present in daily diet are absorbed by rats, pigs [11], and humans [12, 13], and their molecules can incorporate into erythrocyte membranes [14]. Resorcinolic lipids are the group of phenolic lipids with the most precisely defined amphiphilic properties. Values of the HLB (hydrophilic/lipophilic

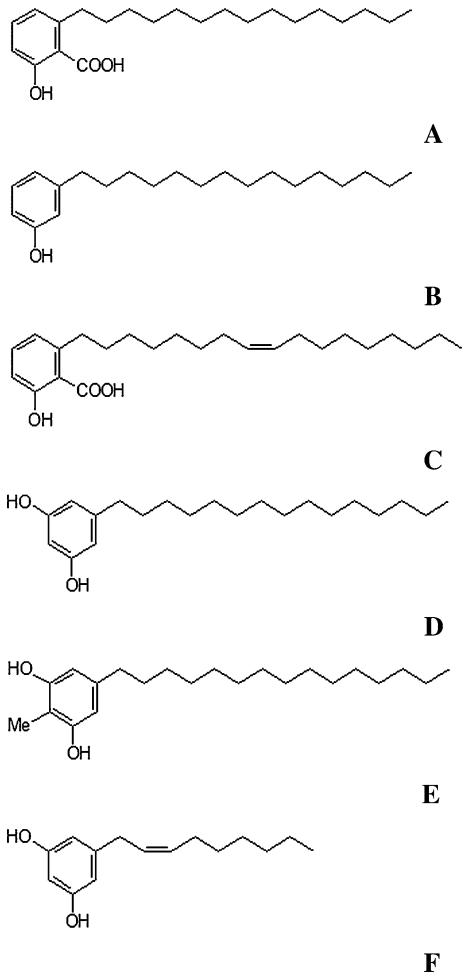

Fig. 1 The representative structures of selected phenolic lipids. **a** Anacardic acid (saturated homologue), **b** cardanol (alkylphenol, saturated homologue), **c** merulinic acid, **d** cardol (saturated homologue), **e** methylcardol (saturated homologue), **f** climacostol

balance) were ~4 for saturated-chain homologues and ~5 for monounsaturated homologues [15]. Their octanol/water partition coefficients (log $P_{o/w}$) are high (7.4, 9.2, and 10.9 for, respectively, homologues C15, C17, and C19) [16], especially compared with that of cardanol (alkylphenol separated from technical CNSL), which is 3.15 [17]. Resorcinolic lipids form stable monomolecular layers at the air–water interface [15, 18], in which the dihydroxybenzene rings of the lipid molecules are oriented perpendicularly to the surface of the subphase [19]. The area occupied by a single molecule depends on both the length of the aliphatic chain and the degree of its unsaturation [15]. This is strongly dependent on the temperature [20] and pH of the subphase buffer [19]. Resorcinolic lipids show very low values for the critical micelle concentration (CMC). The CMCs determined for different homologues in neutral pH by solubilization of 1,6-diphenyl-1,3-5-hexatriene were in the range of 4.5–8.5 μM and depended on the length and saturation of the hydrocarbon chains

(Kieleczawa and Kozubek, unpublished data). The CMCs obtained for long-chain homologues by surface pressure measurements were lower (0.5–2.6 μM) [21].

The lipid aggregates of 3-pentadecylphenol (hydrogenated unsaturated fractions of alkylphenolic oil from CNSL) found in aqueous solution have a micellar character. The results obtained for 3-pentadecylphenol in an equimolar binary water/methanol mixture indicate ordering and consequently cooperative effects in these aggregates. High fluorescence anisotropy was found in aqueous solutions over the whole temperature range between 25 and 55°C, but in pure methanolic solution the anisotropy was generally around zero. It can be concluded that the structural rearrangement in 3-pentadecylphenol aggregates with increasing temperature, causing an increase in the mobility of the phenolic headgroups, a decrease in their tight packing, and, most probably, also an increase in their accessibility by water molecules. As the fluorescence anisotropy remains high, the aggregates remain intact and the observed changes have high similarity to a phase transition [22].

Phenolic lipids are very useful compounds for semisynthesis and their derivatives also have amphiphilic characters. It was demonstrated that 1-sulfate-3-myristoyl-5-pentadecylbenzene (pentadecylresorcinol derivative) is a more hydrophilic compound, with a CMC value of 0.893 μM [23]. A micellization study of 2,4-sodium dissulfonate-5-*n*-pentadecylphenol synthesized from hydrogenated cardanol showed that the CMC depends on temperature and electrolyte (potassium chloride) concentration in the subhase buffer and that it decreased with increasing electrolyte concentration and temperature. Analysis of the Gibbs free energy of micellization indicated that this process was spontaneous for all the studied systems and temperatures [24]. Similarly, the surfactant properties of the polyetoxylate derivatives of cardol, cardanol, and 3-pentadecylphenol were investigated by the reduction of the surface tension of water. The polyetoxylates of cardanol and 3-pentadecyphenol appeared to be similar in surfactancy, but cardol polyetoxylate exhibited a relatively smaller reduction in surface tension [25]. Sodium cardanol sulfonate was found to be useful as an alternative anionic surfactant with a CMC of 0.372 M and a relative detergency of 93.7% compared with dodecylbenzene sulfonate [26].

Phenolic lipids interact with biological membranes and model bilayers

Many important cellular metabolic processes are related to biological membrane structures and depend on their properties. The structure and dynamics of lipid bilayers are crucial for their biological function. Incorporation of foreign compounds, for example, other lipids or drugs, into the bilayer system changes the structure of the bilayer and its biological function. Phenolic lipids exhibit very marked amphiphilic properties and can incorporate into phospholipid bilayers. This process very often causes changes in biological membrane as well as model bilayers and can be investigated by various methods.

Natural bacterial alkylresorcinols present in mixtures with phospholipids stabilized phosphatidylethanolamine, phosphatidylglycerol, and diphosphatidylglycerol black lipid membranes, with the extent of the stabilization dependent on the type of phospholipid [27, 28]. The authors postulated the formation of a structural network of aggregates in phospholipid–resorcinolic lipid mixtures held together by hydrogen bonds between the alkylresorcinol and the polar headgroups of the phospholipids. The interaction of the free hydroxyl groups in the alk(en)ylresorcinol ring with phospholipids through the formation of hydrogen bonds within the membranes was indicated by infrared spectroscopic analysis [29]. This is in agreement with data obtained for dry and hydrated film of 3-pentadecylphenol/dipalmitoylphosphatidylcholine (DPPC). Interaction of these two lipids was studied by ATR–IR (attenuated total reflection infrared spectroscopy). Studies of dry DPPC-pentadecylphenol bilayers showed a strong intermolecular H-bond between the pentadecylphenol phenol group and the DPPC phosphate group which is maintained during hydration. The addition of 3-pentadecylphenol to the pure dry DPPC bilayers decreased the temperature of the main phase transition. When the molar ratio of both lipids was 50%:50%, the T_m decreased from 98°C (for pure dry DPPC bilayer) to 48°C. Data analysis indicates the nature of the phase transition in the 3-pentadecylphenol/DPPC mixtures as a chain-melting phase transition [30]. On the other hand, addition of panosialins A, B, and C, polar arylalkane-type enzyme inhibitors which are widespread among the streptomycetes, to the black lipid membranes' washing electrolyte caused a remarkable increase in membrane current by the formation of ion pores which are responsible for changes of membrane conductance [31].

Phenolic lipid molecules exhibit the ability to self-aggregate spontaneously to a lamellar type of aggregate. Batrakov et al., using bacterial alkylresorcinols, showed that saturated-chain homologues could form stable black lipid membranes [27, 28, 32, 33], especially at high pH (>7.5). Under alkaline conditions, cardol and methylcardol from CNSL form liposomal structures alone as well as in mixtures with cholesterol, fatty acids, or phosphatidylethanolamine. These vesicular structures show relatively high entrapment of the marker molecules and size stability. The retention of the captured solute depends on the type of resorcinolic lipid and the temperature, but it is generally lower than that of control phospholipid liposomes [34].

The effects on the phase behavior of bilayer mixtures of DPPC (dipalmitoylphosphatidylcholine) or MPPC (l-myristoyl-2-palmitoyl-phosphatidylcholine) and 3-pentadecylphenol have been investigated using electron microscopy. These studies revealed the formation of liposomes up to a concentration of 50 mol% 3-pentadecylphenol in DPPC and MPPC. Simultaneously, pure 3-pentadecylphenol in phosphate buffer solution does not form liposomes [22]. ^{31}P NMR investigations showed that a 3-pentadecylphenol/DPPC (50/50 mol%) dispersion adopts a lamellar structure at a temperature below that of the phase transition. At a higher temperature (60°C), above the temperature of the observed phase transition, this system adopts an isotropic phase [35].

Hexylresorcinol is a chemical analogue of microbial anabiosis autoinducers of the alkylhydroxybenzene group. An electron microscopy study of liposomal suspensions provided evidence for an increase in liposome size and their aggregation in response to hexylresorcinol introduction at below-critical concentrations ($2.0–4.75 \times 10^{-4}$ M). Hexylresorcinol at above-critical concentrations (5.0×10^{-4} M and higher) resulted in destruction of the liposomes. When the ratio between this compound and egg lecithin reached or exceeded 1:1, the lipid bilayer was destroyed [36].

An increasing amount of resorcinolic lipids in liposomal membranes made from phosphatidylcholine caused remarkable alteration in the thermotropic properties of phospholipid bilayers. Saturated and unsaturated homologues of these compounds, at low concentrations in the membrane, showed good miscibility with phospholipids. With increasing concentration of alk(en)ylresorcinols in the bilayers, effects related to phase separation were observed and a shift of the main phase transition towards higher temperatures was also noted [37]. At low concentrations in the membrane (5-20 mol%), saturated and monounsaturated C17 homologues showed different effects on the thermotropic properties of hydrated dipalmitoylphosphatidylcholine [38]. At concentrations >10 mol%, the saturated homologue caused a decline in the $L_{\beta'} \rightarrow P_{\beta'}$ pretransition, an increase in temperature, and enthalpy of the main phase transition. The unsaturated homologue caused a shift of the pretransition towards a higher temperature, with broadening of the main transition but lowering of its enthalpy. At a concentration in the membrane above 15 mol% of alk(en)ylresorcinol, a process of phase separation was observed in mixtures of phosphatidylcholine and resorcinolic lipids [37, 38]. These observations were later confirmed by other authors [39].

The presence of 3-pentadecylphenol molecules in the DPPC liposome bilayer caused an increase in T_m proportional to the increase in 3-pentadecylphenol concentration. The temperature of the observed phase transition rose from 41.5°C for DPPC liposomes to 50.9°C for 3-pentadecylphenol/DPPC (50/50 mol%) liposomes. The phase transition observed in 3-pentadecylphenol/DPPC liposomes is connected with a drastic increase in the hydration of the ester groups of DPPC molecules. These changes are greater in the hydration of C = O moieties in the 3-pentadecylphenol/DPPC system than in pure DPPC [35]. These data were confirmed by differential scanning calorimetry. At higher 3-pentadecylphenol concentrations, the calorimetric transition becomes considerably more complex, as several components with different melting point are observed. This can indicate the coexistence of various phases with different compositions [35].

Phenolic lipids can cause significant changes in the biophysical properties of phospholipid bilayer. One of these is disturbance of the molecular packing of the bilayer's components. The presence of incorporated resorcinolic lipids in the bilayer of lecithin vesicles affects the fluidity of the membrane measured by the mobility of spin-labeled fatty acids. At temperatures above the phospholipid phase transition temperature, both saturated and unsaturated homologues at concentrations <6 mol% caused an increase in the order parameter for 5-doxylstearate. At higher concentrations in the lipid membrane (6-14 mol%), the studied homologues also considerably decreased 12-doxylstearate mobility [40]. Resorcinolic lipids showed a much stronger effect on the mobility of both types of markers (5-doxylstearate and 12-doxylstearate mobility) in liposomal membranes containing cholesterol. This cholesterol-like effect of resorcinolic lipids appeared at lower membrane alk(en)yl resorcinol concentrations and was stronger for membranes containing higher cholesterol concentrations [40]. A similar stabilizing effect of alkylresorcinols was observed in a diphosphatidylglycerol bilayer with pyrene as a fluorescent marker [29].

Phenolic lipid molecules act on the liposomal surface charge and the mobility of lipids. Investigations using fluorescein-phosphatidylethanolamine as an indicator of surface-associated processes showed that the intensity of fluorescence of this membrane probe increases during the incorporation of anacardic acid [21] and merulinic acid [41] into egg lecithin liposomes; this effect was visible in media of both low and high ionic strength. This indicates a decrease in the local pH value at the membrane surface. Measurements of the alteration of fluorescence polarization of two types of membrane probes (NBD-PE and TMA-DPH) preincorporated into DPPC liposome bilayers showed that phenolic lipid molecules exhibit different and structurally dependent depths of localization in liposomal membrane. Resorcinolic lipids from rye bran and cardol from CNSL affected the properties of the hydrophobic region of the bilayer, but the properties of the subsurface part of the phospholipid bilayer were altered by anacardic

acid, methylocardol, alkylphenol [21], and merulinic acid [41]. It was also found that 1-sulfate-3-myristoyl-5-pentadecylbenzene, a semisynthetic derivative of 5-*n*-pentadecylresorcinol, intensively quenched the 9-anthroyloxystearic acid signal, which suggests a relatively deep location of these molecules within the lipid bilayer [23]. Similar properties were also shown for cardanol (Stasiuk, unpublished data). Phenolic lipids can be used as potential membrane probes because they show ability for intrinsic fluorescence. The changes in the intrinsic fluorescence of 3-pentadecylphenol indicate that incorporating molecules of this compound into the bilayer changes the ordering in its headgroup region [22].

Phenolic lipids added to media containing liposomes exhibited the ability to induce increased bilayer permeability for ions and small nonelectrolytes [42]. The increased permeability of liposomal membranes induced by resorcinolic lipids may result from the formation of nonbilayer structures within the membrane, such as reversed micelles or hexagonal phase (H_{II} type) [37]. Specificity of the interactions of these compounds with liposomal bilayer was also found. Merulinic acid induced increased permeability of liposomal vesicles depending on the composition of the liposomal bilayer and it was stronger when the lipid bilayer contained glycolipids (monogalactosyldiacylglycerol and digalactosyldiacylglycerol) and sphingomyelin [41]. Pentadecylresorcinol and cardol caused a substantial increase in calcein leakage from large unilamellar vesicles containing glycolipids (monogalactosyldiacylglycerol and digalactosyldiacylglycerol) [21].

The effect of 5-*n*-alkylresorcinols on the properties of phospholipid vesicles depends on their localization asymmetry. A significant increase in bilayer permeability was observed when the title compounds were present only in the external medium. When these amphiphiles were preincorporated into the lecithin bilayer during its formation, the resulting liposomes effectively encapsulated water-soluble solutes, their size was smaller than that of pure lecithin liposomes, and they were more homogeneous and stabile [43]. Cardanol preincorporated into a 1-palmitoyl-2-oleylphosphatydilcholine liposomal bilayer decreased the rate constant of leakage of carboxyfluorescein from the liposomes in the absence of Triton X-100, and insertion of this compound had a stabilizing effect on the corresponding liposomes, which is a cholesterol-like effect [17]. Hexylresorcinol affects the stability of monolamellar liposomes formed of egg phosphatidylcholine. The critical ratio between hexylresorcinol and egg lecithin for liposome protection against the lytic activity of the surfactant Tween 20 was found to be close to equimolar [36]. The dual stabilizing/destabilizing effect of resorcinolic lipids was investigated using atomistic molecular dynamics simulations to elucidate its molecular nature. Studies on the interactions of any of the three resorcinol homologues, differing in alkyl tail length, with dimyristoylphosphatidylcholine lipid bilayers indicated that resorcinols preincorporated into the bilayers induced order within the lipid acyl chains, decreased the hydration of the lipid headgroups, and made the bilayers less permeable to water molecules. Simulations in which resorcinols were incorporated from the aqueous solution into a preformed phospholipid bilayer induced its local disruption, leading to either transient pore formation or even complete desintegration of the bilayer [44].

Resorcinolic lipids added to the external medium induced the leakage of potassium ions from erythrocytes [42] and increased erythrocyte membrane permeability for nonelectrolytes with a molecular diameter of up to 1.4 nm [45]. They also induced higher membrane permeability for water [46]. Increased membrane permeability often results in cell hemolysis [41, 42]. It was demonstrated that there is a relationship between the hemolytic potency of resorcinolic lipid homologues and the length and degree of unsaturation of the aliphatic side chain [45]. Phenolic and resorcinolic lipids isolated from CNSL exhibit a stronger ability to hemolyse erythrocytes than alk(en)ylresorcinols from rye bran. The EH_{50} (effective concentration resulting in 50% lysis of erythrocytes) values obtained for resorcinolic lipids from rye bran were from 39.5 to 74.9 μM (for homologues from C15:0 to C 25:0, respectively), while the same parameter obtained for anacardic acid was 10, for cardol 18, for methylcardol 25, and for cardanol 30 μM. The mechanism of lytic activity of the investigated compounds differed, and all the hemolytic curves for the agents from CNSL were biphasic, contrary to those demonstrated for the resorcinolic lipids from rye bran [21]. Merulinic acid seems to be the most potent lytic agent of all the investigated phenolic lipids (EH_{50} of 5 μM) [41].

The effect of phenolic lipids and their derivatives on the barrier functions of biological membranes is modulated by the presence of divalent cations that protect erythrocytes against the lytic action of resorcinolic [41, 47, 48] as well as phenolic lipids [21]. The extent of the erythrocyte protection is dependent on both the type of cation and the type of resorcinolic lipid, although Zn^{2+} ions have been found to be the most active in antihemolytic protection.

Studies hitherto showed that all the investigated phenolic and resorcinolic lipids at sublytic concentrations protect erythrocytes against lysis in hypo-osmotic conditions. The lowest protection was shown by anacardic acid and resorcinolic lipids from rye bran [21]. The most effective antilytic agent was cardol at a concentration of 5 μM, inhibiting more than 50% of lysis. Methylcardol and alkylphenol showed intermediate activity [21], similar to that demonstrated by merulinic acid [41].

Experiments using "freeze fracture" electron microscopy showed that changes in the distribution of proteins on the membrane surface occurred after incubation of erythrocytes with resorcinolic lipids. Pentadecylresorcinol caused noticeable aggregation and clustering of protein particles in the membrane. Unsaturated homologues, the compounds with the highest hemolytic activity, generated almost complete disruption of the membrane structure, with aggregation and separation of the membrane protein particles. Long-chain saturated homologues exhibit the weakest effects on membrane morphology [37].

Due to their very high buffer-membrane partition coefficients and low CMCs, the effect of resorcinolic lipids added to the external medium was different from that observed when they were present internally in the membrane. The same homologues showed high hemolytic activity in free form when present in the medium, but were not lytic when introduced in the form of phosphatidylcholine-resorcinolic lipid liposomes, which indicates that the direct exchange of resorcinolic lipids between membranes is limited. This phenomenon was shown for merulinic acid [41] and alkylresorcinol homologues from rye bran (Mania and Stasiuk, unpublished data).

Phenolic lipids can interact with other cellular membranes. The interaction of phenolic lipids with cellular and organellar membranes can lead to the inhibition of integral membrane protein activities. Phenolic lipids have been reported to inhibit Ca^{2+}-ATPase of sarcoplasmic reticulum and plasma membrane Ca^{2+}-ATPase. Alkylphenols were found to inhibit plasma membrane Ca^{2+}-ATPase, with 2-nonylphenol being the most potent compound of a series of synthetic phenols. Several bis-resorcinols isolated from the Australian plants *Grevillea robusta* and *G. striata* and their synthetic analogues also showed inhibitive properties against Ca^{2+}-ATPase activity. The proposed mechanism of action of these inhibitors depends on their highly lipophilic nature; they would interact with the hydrophobic interior or at the lipid–protein interface, thereby perturbing Ca^{2+}-ATPase enzyme function [49].

The hydroxy- or dihydroxybenzene ring present in the phenolic lipid molecule suggests the possibility of replacing these compounds, such as ubiquinone or plastoquinone, in mediating processes of electron and proton transport. Long-chain resorcinolic lipids (C10, C19) at a concentration of 10^{-4} M inhibited the respiration of yeast cells [15, 50], *Bacillus cereus*, *Micrococcus lysodeicticus* [29], and thymocytes [51]. Long-chain alkylresorcinols also inhibited the oxidation of NAD-dependent substrates in isolated mitochondria [52, 53]. Climacostol induced morphological changes in rat liver mitochondria and inhibited NAD-linked respiration, with no apparent effect on succinate-linked respiration in submitochondrial particles. This suggests that this compound specifically exerts its action on the respiratory chain complex I [54]. The possibility of some uncoupler properties of phenolic lipids was demonstrated for both resorcinolic lipids from rye grain [55] and anacardic acids [56]. Anacardic acids exhibited uncoupling effects similar to the classical uncoupler 2,4-dinitrophenol. The most effective of these compounds for uncoupling was anacardic acid with a C15:1 side chain. When the carboxyl group in anacardic acids was lost, when converting them to the corresponding cardanols, the uncoupling activity dramatically decreased, regardless of the number of double bonds in the long alkyl chain. These results suggest that the C15 alkyl side chain as well as the carboxyl group may play an important role in assisting the uncoupling activity of anacardic acids in liver mitochondria of animals [56]. Further studies using liposomes as a model membrane and a cyanine dye and 9-aminoacridine to determine changes in membrane potential and pH difference, respectively, showed that the anacardic acids may have a unique function and could behave as both an electrogenic (negative) charge carrier and a "proton carrier" that dissipates the formed transmembrane proton gradient. It was proposed that the anacardic acid anion, in the same way as the protonated form, is able to permeate the lipid bilayer freely and act as a (negative) charge carrier. This is highly likely given that the dissociated carboxylic group of anacardic acid is able to form intramolecular hydrogen bonding with a neighboring hydroxyl group to delocalize the negative charge [57].

Due to the amphiphilic properties of phenolic lipids, a significant part of their effect is related to their interaction with membranous structures and the hydrophobic domains of proteins. These interactions seem to be mainly nonspecific. Phenolic lipids' action on a cell is comprehensive, which will be described below.

Biological activity of phenolic lipids

The amount of data describing the various biological activities of phenolic lipids has been increasing in the last few years, but our understanding of the biological function of these compounds and the detailed mechanism of their effects on cellular processes is still incomplete.

Phenolic lipids affect oxidation processes

The generation of free radicals, including reactive oxygen species (ROS), is an inevitable phenomenon associated with the aerobic lifestyle. A prerequisite for the function and development of cells in an oxygen-containing environment is the presence of protective systems involving specialized enzymes and low-molecular-weight antioxidants. Phenolic compounds seem to be efficient

nonenzymatic protectors against oxidative stress. They can act as antioxidants in a variety ways. They can prevent the ions of transition metals from initiating oxidation, quench the intermediates of oxidation (including ROS), and inhibit various prooxidant enzymes.

Anacardic acids are able to chelate divalent metal ions, such as Fe^{2+} and Cu^{2+} [58, 59], and have high selectivity toward transition metal ions, especially Fe^{2+} and Cu^{2+} [60]. They may prevent cell damage induced by H_2O_2 since this can be converted to a more ROS in the presence of these metal ions [61].

Phenols are able to donate the hydrogen atom of the phenolic OH to free radicals, thus stopping the propagation chain during the oxidation process. The mechanism of the antioxidant action of phenolic lipids under physiological conditions may include the formation of an intermediate, 1,2,4-trihydroxy-6-alkylbenzene, as the first product of oxidation. This compound, in turn, due to the easy formation of *o*- and *p*-quinones, may subsequently act as a more effective antioxidant [62]. The alkyl chain connecting the phenolic ring and the carboxylic or alcohol group in phenolic derivatives may stabilize the radical formed during oxidation. The length of the aliphatic side chain plays an important role in the antioxidant activity of resorcinolic lipids. Orcinol exhibits antioxidant activity at a concentration at least ten times greater than that of 1,3-dihydroxy-5-pentadecylbenzene and higher homologues isolated from cereal grains [63]. Olivetol exhibits good antioxidant activity against the non-isothermal autoxidation of linolenic acid [64].

Long-chain 5-*n*-alk(en)ylresorcinol homologues prevent the Fe^{2+}-induced peroxidation of fatty acids and phospholipids in liposomal membrane [65] and autoxidation processes in triglycerides and fatty acids [66, 67]. At a millimolar concentration, alkylresorcinols from bacteria [68] and cereal grain [63] inhibited Fe^{2+}-ascorbic acid and Fe^{2+}-NADPH-induced peroxidation of liver microsomes completely and that of the sarcoplasmic reticulum partially. They have also been effective in protecting the erythrocyte membrane against hydrogen peroxide-induced oxidation [69]. The antioxidant properties of rye bran alkylresorcinols were also evaluated using their radical-scavenging activity on DPPH (2,2-diphenyl-1-picrylhydrazyl) and the chemiluminescence method (CL). DPPH radical reduction varied from ~10 to ~60% for the alkylresorcinol homologues at concentrations of 5–300 μM and was not dependent on the length of the alkyl side chain of the particular homologue. Values of EC_{50} for all the alkylresorcinol homologues were significantly higher than those for Trolox and α-, δ-, and γ-tocopherols used as positive controls. CL inhibition was evaluated for all the tested alkylresorcinol homologues at concentrations of 5 and 10 μM and varied from ~27 to ~77%. Similar to the DPPH method, the slight differences in CL inhibition suggest that the length of the alkyl side chain had no major impact on their antioxidant properties [70]. These results were confirmed by a further investigation. 5-*n*-alkylresorcinols (C15:0, C17:0, C19:0, C21:0, and C23:0) did not exert potent antioxidant activity in the FRAP (ferric reduction ability of plasma) and DPPH radical assays. However, they were able to significantly inhibit copper-mediated oxidation of human low-density lipoprotein in vitro and to increase the self-protective capacity of HT29 human colon cancer cells against DNA damage induced by hydrogen peroxide and genotoxic fecal water samples [71]. The precise mechanisms of the protective effect of resorcinolic lipids on cellular structures from oxidation are still unknown. There are some reports showing that the radical-scavenging and hydrogen-donating powers of pentadecylresorcinol were low [72].

Studies on the antioxidant activities of three short-chain pyrocatechol derivatives indicate that 3,4-dihydroxybenzylic alcohol, 2-(3,4-dihydroxyphenyl)ethanol, and 3-(3,4-dihydroxyphenyl)-1-propanol inhibit the DPPH reaction by over 80%. It can also be observed that increasing the length of the alkyl chain increases the radical-scavenging capacity [73].

Phenolic lipids present in CNSL also show antioxidant activities. A mixture of anacardic acids showed higher antioxidant capacity than cardols and cardanols. Anacardic acid containing three double bonds in the alkyl side-chain confers greater antioxidant and enzyme inhibition capacity than the other acids possessing 1-2 double bonds. The antioxidant capacity of anacardic acids is related more to the inhibition of superoxide generation and xanthine oxidase than to scavenging of hydroxyl radicals [74]. On the other hand, immature CNSL (iCNSL) demonstrated antioxidant activity against radical scavengers that trap peroxy radicals [75]. iCNSL was also studied in vivo using a *Saccharomyces cerevisiae* assay to qualify its antioxidant activity. Incubation of the strains with iCNSL resulted in increased survival after H_2O_2 treatment for strains of *S. cerevisiae* defective in antioxidant defense [76]. This is in agreement with an earlier investigation which demonstrated that fresh cashew apple juice and processed juice also have antioxidant and antimutagenic properties against hydrogen peroxide [77]. Investigations of oxygen consumption by hydrogenated cardol, hydrocardanol, and its derivatives during reaction with peroxyl radical showed that cardanol represents a renewable, low-cost, and convenient alternative source for a number of products with good antioxidant properties [78]. Studies on the antioxidant capacity of cashew apple, nut (raw and roasted), and cashew nut shell liquid showed that the order of inhibitory potency was: cashew nut shell liquid (about 100% inhibition), the hexane extract of cashew fiber (94%), and cashew

apple (53%). A mixture of anacardic acids showed higher antioxidant capacity compared with cardols and cardanols [74].

C7-alkylhydroxybenzene, a chemical analogue of a microbial anabiosis autoregulator, protects yeast cells from ROS produced under gamma irradiation. This effect manifested both in the preservation of cell viability during irradiation and in the recovery of their capacity to proliferate after irradiation. The protective mechanism of C7-alkylhydroxybenzene involves the scavenging of ROS resulting from oxidative stress [79]. C7-alkylhydroxybenzene also showed an ability to protect cells against photooxidation [80]. The effect of alkylhydroxybenzenes on the resistance of *S. cerevisiae* cells to heat shock and oxidative stress of lethal intensity depended on the hydrophobicity of the investigated compounds; C7-alkylhydroxybenzene at concentrations of 0.25–0.5 g/l caused a two- to fivefold increase in the resistance of yeast cells to hydrogen peroxide, whereas C12-alkylhydroxybenzene reduced it at all concentrations. C7-alkylhydroxybenzene and C12-alkylhydroxybenzene had a similar effect on yeast subjected to heat shock [81].

Phenolic lipids can modulate the activities of enzymes involved in the formation of free radicals in the human body under physiological conditions. These enzymes include lipoxygenases and cyclooxygenases (involved in the enzymatic oxidation of lipids leading to the formation leukotrienes, thromboxanes, and prostaglandins). Another example of this type of enzyme is xanthine oxidase, which plays an important role in the catabolism of purines, catalyzing the oxidation of hypoxanthine to xanthine, and can further catalyze the oxidation of xanthine to uric acid.

Leukocytic lipoxygenase (5-LOX)-catalyzed oxidation of arachidonic acid is effectively inhibited (by 90%) by polyunsaturated pentadecylresorcinol homologues [82]. Long-chain 5-*n*-alkylresorcinol homologues also showed high inhibitory potencies against soybean lipoxygenase isoenzymes [83, 84], which were dependent on both chain length and on the degree of side-chain unsaturation as well as on the isoenzyme studied and the substrate used. The soybean lipoxygenase-1-catalyzed oxidation of linoleic acid was inhibited by anacardic acid (C15:1). The inhibition kinetics indicates that anacardic acid is a competitive inhibitor [85, 86]. This activity is largely dependent on the nature of the alkyl side chains present in anacardic acid molecules [87]. The LOX inhibition is attributed to the ability of anacardic acids to chelate iron in the enzyme. Thus, anacardic acids chelate iron in the active site of the enzyme and then the hydrophobic tail portion slowly begins to interact with the hydrophobic domain close to the active site. The formation of the anacardic acid-ferric ion complex was detected at a ratio of 2:1 [59]. 5-(11′Z-heptadecenyl)-resorcinol and 5-(8′Z,11′Z-heptadecadienyl)-resorcinol isolated from mango peels exhibited a weak ability to inhibit of 5-lipoxygenase-catalyzed leukotriene formation, but these compounds were found to be very potent inhibitors of cyclooxygenase COX-1 and COX-2. Structure–activity studies with reference to synthetic saturated homologues indicated that the degree of unsaturation in the alkyl chain played a key role in COX inhibitory activity, whereas the influence of chain length was less significant [88]. The alkylresorcinol concentration affects the amount of synthesized thromboxane A in platelets; high and low concentrations stimulated, whereas average concentrations inhibited this process [89]. On the other hand, it was demonstrated that long-chain alkadien(trien)ylphenols (i.e., cardanols, cardols, and anacardic acids) as well as their derivatives were oxygenated by soybean lipoxygenase-1 [90].

Hypoxanthine/xanthine oxidase is an enzyme involved in purine metabolism. Xanthine oxidase inhibitors are useful in treating some diseases such as gout and urate calculus by regulating uric acid formation. Anacardic acids inhibit the generation of superoxide radicals by xanthine oxidase [74, 91] without radical-scavenging activity [86]. The results indicate that anacardic acid binds to allosteric sites near the xanthine-binding domain in xanthine oxidase [91].

Phenolic lipids are involved in interactions with DNA

The antioxidant properties of phenolic lipids, manifested as the ability to scavenge radicals and inhibit enzymes involved in the generation of free radicals under physiological conditions, suggest the possible participation of these compounds in the protection of cells against carcinogenesis. Xenobiotics which induce mutagenic processes are activated in many cases by oxidation processes. Alkylresorcinols exhibit an absence of mutagenic, carcinogenic, and cocarcinogenic effects [92]. This could suggest their possible application in pharmacology and medicine [93]. A preparation comprising a mixture of predominantly saturated-chain homologues (C15–C27) drastically inhibited the effect of direct and indirect (metabolically activated) mutagens. The effect was strongest in the case of the indirect-acting mutagens benzo[*a*]pyrene and 2-aminofluorene, for which more than 50% inhibition was observed. For direct-acting mutagens, such as methyl methanesulfonate and daunorubicin, the effect of resorcinolic lipids was smaller. In the sister chromatid exchange (SCE) test with in vitro cultured human blood-derived lymphocytes, a significant decrease in SCE frequency induced by benzo[*a*]pyrene was also observed [94]. This was confirmed in further experiments using a cytokinesis-blocked micronucleus assay and a thioguanine-resistance test. Resorcinolic lipids significantly decreased the rate and

frequency of mutations induced in lymphocytes cultured with benzo[*a*]pyrene and mitomycin C [95]. Antimutagenic activity was also shown for phenolic lipids present in fresh unprocessed and processed juice of the cashew tree. The antimutagenic properties against the direct mutagens methyl methanesulfonate and 4-nitroquinoline-*N*-oxide and the indirect mutagen benzo[*a*]pyrene were investigated using pre-treatment, co-treatment, and post-treatment assays with *Salmonella typhimurium* strains. The results suggest that both fresh and processed cashew apple juice can protect the cells against mutagenesis [96]. An anti-genotoxic effect was shown for 5-*n*-alkylresorcinols in HT29 human colon cancer cells. DNA damage induced by hydrogen peroxide was significantly reduced and a response to the chain length was observed. The decrease in genotoxicity was approximately 40% with pentadecylresorcinol and 10% with heneicosylresorcinol [71]. Methylresorcinol and hexylresorcinol enhanced the UV resistance of various DNA molecules of different origin and conformation (the linear DNA of the λ phage, bovine spleen DNA, and the DNA of the pUC19 plasmid). The destruction of DNA by irradiation with UV light in the presence of the investigated compounds was comparatively insignificant and depended on the chemical structure and the concentration of the compound. Studies using pUC19 plasmid demonstrated that the investigated alkylresircinols prevented both the supercoiled annular-supercoiled relaxed and the supercoiled relaxed-linearized transitions [97].

The action of resorcinolic lipids on cells could be a consequence of their effect on the structure and metabolism of nucleic acids. It was shown that merulinic acid at a concentration of 100 μg/ml completely inhibited the synthesis of DNA and RNA and protein synthesis in *Bacillus brevis* cells [98]. Similar inhibitory properties have been shown for 5-*n*-decylresorcinol in isolated rat thymocytes [51].

Resorcinolic lipids possess the ability of DNA strand scission. 5-*n*-tridecyl and 5-*n*-pentadecenylresorcinols present in an extract of the plant *Hakea* sp. exhibited the ability of Cu^{2+}-induced scission of the replicating strand in plasmid DNA φX174 [99, 100]. In addition, several bis-(dihydroxyalkylbenzenes) were also capable of mediating Cu^{2+}-dependent DNA cleavage [101]. The activity of resorcinolic lipids increases with increasing number of carbon atoms in the aliphatic chains [102]. This suggests that the alkylresorcinol molecules interact with the double helix of DNA by the intercalation of chains in its interior. The alkylresorcinol-induced nucleic acid strand scission is related to the generation of hydroxyl radicals mediated by oxidation at high pH in the presence of Cu^{2+}, O_2, and alkylresorcinol [102]. Alkylresorcinol activity increased in the presence of oxygen, which suggests that DNA cleavage by 5-*n*-alkylresorcinols involves oxygenation of the benzene ring to trihydroxy derivatives capable of reducing copper for the subsequent formation of ROS. The hydroxyquinone products, derived from 1,2,4-trihydroxy-6-alkylbenzene, formed during oxidation of the alkylresorcinol afford catecholic moieties that were proposed to coordinate Cu^{2+} and subsequently affect the reduction of dioxygen to reactive species followed by the oxidation of the catecholic moiety via the coordinated Cu^{2+} ion [100, 102]. DNA cleavage was not a sequence-specific process. It has to be noted that the actual role of Cu^{2+} ion in the DNA strand scission activity of these natural products is not fully understood at present. Studies on the ability to cleave DNA by phenolic acid amides, alkycatechol derivatives of a crude extract from *Piper caninum*, showed that *N-cis*-feruloyl tyramine and *N*-trans-feruloyl tyramine induce the relaxation of supercoiled pBR322 plasmid DNA in the presence of Cu^{2+}; however, neither of these compounds contains a catechol moiety (one of a hydroxyl group is modified by a methyl moiety) [103].

Cytotoxicity of phenolic lipids

It has been documented that a variety of constituents isolated from food and herbal plants have sometimes proved to be anticarcinogenic and antimutagenic. In recent years, phenolic lipids have attracted attention for their potential use in the therapy and/or prevention of specific classes of diseases. Phenolic lipids, mainly resorcinolic lipids, possess an ability of Cu^{2+}-induced DNA strand scission. In parallel, they exhibit a lack of mutagenic, carcinogenic, and cocarcinogenic effects and protect DNA against hydrogen peroxide- and UV-induced damage. Due to all these properties, phenolic lipids were intensively investigated as cytotoxic and antitumor agents.

Studies on the biological activity of 5-pentadecenylresorcinols isolated from *Ginkgo biloba* indicated their strong antitumor activity against S180 tumor in mice. The active component, 5-*n*-pentadec-8-enylresorcinol, caused almost complete inhibition of tumor cell growth [104]. Similar activity was observed for the alkenylresorcinol against P-338 leukemia cells [105]. The presence of a carboxyl group in the resorcinol ring is not obligatory for the antitumor activity, as found previously for antibacterial activity [106]. A preliminary evaluation of the potential antitumor-promoting activities of 5-alk(en)ylresorcinols from Gramineae bran oils showed that the investigated compounds exhibited only a moderate activity against the induction of Epstein–Barr virus early antigen, and it was observed that increasing the chain length resulted in decreasing the activity, as was found for the 5-*n*-alkylresorcinols [107].

The induction of apoptosis is known to be an efficient strategy in cancer therapy. Distinctive events of apoptosis

are appreciable cytoplasmic shrinkage, condensation of chromatin, cleavage of DNA into 180–200 bp nucleosomal units, activation of proteolytic enzymes known as caspases, and disintegration of the cell into small fragments [108]. On the other hand, there are some kinds of programmed cell death which do not exhibit all these processes. Apoptosis-like programmed cell death can be realized, for example, in a caspase-independent manner or with large-scale DNA fragmentation. It was shown that climacostol, a natural toxin isolated from the freshwater ciliated protozoan *Climacostomum virens* and belonging to the group of resorcinolic lipids, effectively inhibited the growth of tumor cell lines (human tumor squamous carcinoma A431 and human promyelocytic leukemia HL60) in a dose-dependent manner by inducing programmed cell death, while non-tumor human endothelial EA.hy926 cells appeared to be substantially resistant to this molecule. The mechanism of action of climacostol on the tumor cell lines does not appear to be necrosis based, but to involve apoptosis (HL60 cells) or apoptosis-like (A431 cells) programmed cell death. Climacostol treatment of A431 and HL60 cells induces the externalization of phosphatidylserine (a characteristic feature of apoptotic programmed cell death is the loss of phospholipid asymmetry and the exposition of phosphatidylserine on the outer layer of the plasma membrane), which increases in a time- and dose-dependent manner. In contrast, climacostol did not induce phosphatidylserine exposure in EA.hy926 control cells [109]. Ginkolic acids induced programmed death of cultured chick embryonic neurons without oligonucleosomal DNA fragmentation and caspase-3 activation [110].

5-(2′-oxoheptadecyl)-resorcinol and 5-(2′-oxononadecyl)-resorcinol isolated from the fermentation of an imperfect basidiomycete exhibited cytotoxic effects against the human colon tumor cell lines COLO-320, DLD-1, and HT-29, the human promyeloid leukemia cell line HL-60, the human leukemia T cell JURKAT, the human hepatocellular carcinoma cell line HEP-G2, and the J774 mouse macrophage cell line. These compounds induced morphological and physiological differentiation of HL-60 cells into granulocytes, which subsequently died by apoptosis [111]. Apoptotic cell death was investigated using methanol [112] and dichloromethane [113] extracts of *Lithraea molleoides* (Anacardiaceae) as well as pure 1,3-dihydroxy-5-(tridec-4′,7′-dienyl)benzene isolated from *L. molleoides* leaves [113, 114]. The tested extracts and compound showed cytotoxic activity on human hepatocellular carcinoma HepG2 cells [112, 114], Hep3B cells [114], and mucoepidermoid pulmonary carcinoma H292 and mammary gland adenocarcinoma MCF7 cells [113]. After 24 h of 5-alkylresorcinol treatment, both hepatocellular carcinoma cell lines showed the typical morphological alterations of apoptosis, DNA fragmentation, and condensed and fragmented nuclei. The cytotoxic effect of 5-alkylresorcinol on these cell line was independent of their p53 or Fas phenotypic profile [114].

Effective induction of apoptotic cell death of Mahlavu cells (poorly differentiated p53 mutants of a human hepatoma subline, highly refractory to a number of chemotherapeutic agents and radiotherapy due to their high expressions of multidrug resistance gene-1 and Bcl-2 proteins) via an oxidative stress-mediated caspase-dependent mechanism was observed after treatment of the cells with 6-shogaol. 6-shogaol, an alkanone isolated from the rhizomes of ginger, also causes a depletion of intracellular glutathione content and a significant drop in mitochondrial transmembrane potential [115].

Resorcinolic lipids were also found to potentate the action of the anti-tumor drugs bleomycin and cisplatin [100]. Anacardic acid potentiates apoptosis induced by tumor necrosis factor and chemotherapeutic agents and may thus have potential as an anticancer agent. This compound down-regulates the expression of NF-κB-dependent gene products involved in cell proliferation, anti-apoptosis, invasion, and angiogenesis [116].

Electron microscopic analysis of the human keratinocyte cell line HaCaT treated with gingkolic acids showed morphological changes, indicating that the cytotoxic activity of gingkolic acids in these cells is primarily mediated by transformation of the mitochondria. A concentration-dependent release of lactate dehydrogenase after incubation of the cells in the presence of gingkolic acids was also shown, but no release of acidic phosphatase was observed [117]. Ginkgolic acids also have neurotoxic effects and killed cultured chick embryonic neurons in a concentration-dependent manner in the presence and absence of serum. Ginkgolic acid-induced death showed signs of apoptosis as well as of necrosis [110]. Anacardic acids were found to be moderate cytotoxic agents, affecting the growth of BT-20 breast and HeLa epithelioid cervix carcinoma cells [118].

The cytotoxic and genotoxic effects of anacardic acid isolated from the bark of *Amphipterygium adstringens* on CD1 male mice were determined by micronucleus assay. The ratios of polychromatic to normochromatic erythrocytes in mice treated with anacardic acid after 72 h were reduced at all tested dose levels. Anacardic acid did not lead to chromosome damage at the evaluated doses [119]. Anacardic acid and ginkgolic acid are also responsible for the cytotoxic activity of *Ozoroa insignis* bark extract against Hep-G2 (human hepatocellular carcinoma), MDAMB-231 (human mammary adenocarcinoma), and 5637 (human primary bladder carcinoma) cells [120]. Anacardic acids isolated by bioassay-guided fractionation from a culture of the endophytic *Streptomyces laceyi* MS53

exhibited modest cytotoxicity against a human breast cancer cell line (SKBR3) [121].

Phenolic lipids inhibit bacterial, fungal, protozoan, and parasite growth

The interactions of phenolic lipids with biological membranes and DNA structure and cytotoxic activity correspond with their antimicrobial and antiparasitic activity. The first reports concerning the antibacterial action of alkyl derivatives of resorcinols and their use in treating infections appeared in the 1920s. Subsequent investigations indicated that the antibacterial action of extracts from many plants (e.g., *G. biloba* fruit, *Ardisia japonica* plant, seed covers of *Myristica fragrans*) or CNSL is a consequence of the effect of phenolic lipids present in them.

5-alkylresorcinols isolated from the mushroom *Merulius incarnatus* inhibit methicillin-resistant *Staphylococcus aureus* [122]. Resorcinolic lipids produced by *Pseudomonas carboxydoflava* inhibit the growth of other bacteria, such as *Micrococcus lysodeictius* and *Bacillus subtilis* [29, 68]. 5-*n*-pentadecylresorcinols with different degrees of aliphatic chain unsaturation exhibited strong activity towards *Streptococcus mutans*, a bacterium responsible for paradonthosis, and *Propionibacterium acne*, the bacterium that causes acne [123, 124]. The most potent inhibitor was the homologue with an unsaturated aliphatic chain. The presence of carboxylic groups in the ring increased the antibacterial activity remarkably and the bactericidal activity of 4-*n*-hexylresorcinol toward *S. mutans* was less pronounced [125].

Phenolic compounds present in CSNL exhibited potent antibacterial activity against *Bacillus subtilis* and showed only weak activity against *Penicillium chrysogenum* [123]. The bactericidal activity of a series of anacardic acids possessing different side-chain lengths depended on both the bacteria strain and the chemical structure of the anacardic acid [126]. The anacardic acids isolated from the cashew apple exhibited potent antibacterial activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* strains [127, 128]. The antimicrobial activity of CNSL and anacardic acids was tested against several strains responsible for cutaneous infection. CNSL exhibited inhibitory activity against *Propionibacterium acne*, *Corynebacterium xerosis*, and various strains of *S. aureus*, but was not active against the fungus *Pityrosporum ovale* [129]. Studies on the relationship between structure and antibacterial activity of anacardic acids against Gram-positive bacteria, with emphasis on methicillin-resistant *S. aureus* strain, showed that unsaturation in the alkyl side chain is not essential in eliciting activity, but it is associated with increasing the activity. The antibacterial activity of methicillin against *S. aureus* strains was significantly enhanced in combination with C12:0 anacardic acid [130]. The synergistic effects of anacardic acids in combination with methicillin against *S. aureus* strain was confirmed in further investigations. This effect was found to be related to both the length and the unsaturation of the alkyl side chain, and decreased with increasing number of double bonds in the alkyl chain. This effect increased with increasing alkyl chain length up to a maximum of around 10–12 carbon atoms, and then dropped with the addition of further carbons to the chain [131]. Studies on the mechanisms of the bactericidal activity of anacardic acids against methicillin-resistant *S. aureus* indicated that biochemical and metabolic interactions are little involved in the observed processes. It was demonstrated earlier that anacardic acids do not induce chromosome damage in vivo [119] and exhibit an ability to chelate Fe^{2+} and Cu^{2+} [132], which can reduce their bioavailability for bacteria. Anacardic acids are factors which inhibit bacterial respiration by inhibiting the respiratory chain [29]. A recent hypothesis about the mechanism of the antibacterial activity of anacardic acids on methicillin-resistant *S. aureus* proposes that the most important effect is disordering the membrane of the bacteria [133]. The antimicrobial activity of anacardic acids against strains of *S. aureus* sensitive or resistant to penicillin, oxacillin, and methicillin antibiotics is interesting. Moreover, these activities are accompanied by their intrinsic β-lactamase-inhibiting activity. Marked growth inhibition of two strains of *S. aureus* resistant to penicillin by the synthesis of β-lactamase was observed after CNSL and anacardic acids were added at concentrations without antimicrobial activity [129].

Anacardic acids and cardanol from crude extracts of ginkgo fruits exhibited growth inhibition of the Gram-positive bacterium *Bacillus subtilis*, but the sensitivity of the Gram-negative bacterium *Escherichia coli* to anacardic acids and their derivatives was expectedly far lower than that of *B. subtilis* [134]. Studies on the efficiency of anacardic acid as a preservative in tomato products showed that this compound was active against both Gram-positive and Gram-negative bacteria (*Staphylococcus aureus*, *B. subtilis*, and *Escherichia coli* were tested). This indicates that anacardic acid can be considered an alternative natural preservative to synthetic preservatives [135].

Anacardic acids from the cashew apple exhibited antibacterial activity against the Gram-negative bacterium *Helicobacter pylori*. The activity gradually decreased with side-chain length [136]. An anacardic acid mixture isolated from *Amphipterygium adstringens* exhibited a potent dose-dependent antibacterial activity against *H. pylori* with a value in the inhibitory range of reference antibiotics used to test antimicrobial susceptibility and the eradication of

H. pylori [137]. Anacardic acids isolated from the cashew apple also exhibited antibacterial activity against *Streptococcus mutans* [138, 139]. Embelin, a benzoquinone-derivative isolated from an Argentinean collection of *Oxalis erythrorhiza*, presented an inhibitory effect on methicillin-resistant *Staphylococcus aureus* and *Escherichia coli* [140]. The same compound isolated from *Embelia ribes* showed significant antibacterial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Shigella flexneri*, *S. sonnei*, and *Pseudomonas aeruginosa*, and moderate activity against *Salmonella typhi*, *S. boydii*, and *Proteus mirabilis* [141].

On the other hand, resorcinolic lipids are also present in bacterial cells as autoregulators. El'-Registan et al. demonstrated that extracellular autologous regulators of the development of microbial cultures, which control the transition to the stationary stage and the formation of dormant cells (throughout the cycles of culture development and during starvation), may act as adaptogens [142, 143]. In many microorganisms, these metabolites are known to be autologous inducers of anabiosis and have the structure of alkyl hydroxybenzene isomers or homologues [144, 145]. By virtue of their ability to stabilize protein structure [146], they exert membrane-tropic effects [29]. They play an important role in stress responses by increasing cell resistance to chemical and physical factors [147]. The addition of hexylresorcinol during the exponential growth phase of cultures grown on balanced media resulted in cell-division arrest and accelerated the transition to the stationary phase [148]. On the other hand, it was demonstrated that hexylresorcinol cannot prevent the B → A transition in the DNA molecule (the DNA is in the B form in vegetative cells and converts to the A conformation in the endospores during the development of their dormant state). The authors proposed that stimulation of the B → A transition can result from the formation of micella-like nanostructures around DNA macromolecules by the interacting hexylresorcinol molecules [149]. A similar stabilizing effect was shown for *Saccharomyces cerevisiae* [81].

Resorcinolic lipid synthesis is essential for mature cyst formation in *Azotobacter vinelandii*. In the mature cyst, these lipids replace the membrane phospholipids and are also components of the layers covering the cyst. The *arsB* mutant, deprived of the possibility, only to synthesize an alkylresorcinol synthase, produced no resorcinolic lipids. Transmission electron microscopy showed that the mutant formed no mature cysts [150]. Further investigations using a mutant strain carrying an *arsA* mutation indicated that the ArsA protein is essential for the synthesis of these phenolic lipids. The *arsA* mutants were able to form cysts resistant to desiccation. These data could suggest that alkylresorcinols play a structural role in the exine layer of the cysts, but they are not essential for either cyst formation or desiccation resistance [151].

Alkylresorcinol present in the medium also affects endogenous alkylresorcinols synthesis. It was found that when 5-*n*-pentadecylresorcinol was present in the growth medium, the more endogenous alkylresorcinols were synthesized and a drop in the amount of phospholipids was observed [152]. This effect could suggest that alkylresorcinols may act as small hormone-like molecules termed autoinducers and play a role in chemical communication (quorum-sensing) between bacteria cells. This phenomenon was demonstrated earlier in several natural compounds [153, 154].

Phenolic lipids exhibit fungistatic properties similar to their antibacterial activity. The presence of 5-*n*-(heptadec-12-enyl) and 5-*n*-pentadecylresorcinols in the peel was considered responsible for the resistance of mango fruits to fungal infection by *Alternaria alternata* [155, 156] and *Colletotrichum gloeosporioides* [157]. Similarly, the resistance of barley seeds to the pathogenic fungi *Aspergillus niger* and *Penicillium crysogenum* was attributed to resorcinolic lipids present in the seed's epicuticular wax [158]. 5-methylresorcinol present in pericarp wax also protects the kernel against *Aspergillus flavus* infection and aflatoxin production [159]. Aflatoxin production is also inhibited by fresh and processed cashew apple juice [160]. 5-*n*-pentadecylresorcinols and the 5-*n*-alkylresorcinol mixture from rye inhibited the growth of *Aspergillus parasiticus*, *A. versicolor*, *Penicillinum chyrysogenum*, and *P. roqueforte* [161] as well as *Fusarium culmorum*, *Rhizoctonia cerealis*, and *R. solani* [162]. Anacardic acids, cardol, and cardanol from the crude extracts of ginkgo fruits showed motility inhibition followed by lysis of zoospores of the phytopathogenic *Aphanomyces cochlioides* [134]. It was also shown that benzoquinone embelin isolated from *Oxalis erythrorhiza* exhibited an inhibitory effect on the dermatophytic fungi *Epidermophyton floccosum*, *Microsporum canis*, *M. gypseum*, *Trichophyton mentagrophytes*, and *T. rubrum*, with minimal inhibitory concentrations ranging between 50 and 100 μg/ml [140].

3-heptadecyl-5-methoxyphenol isolated from *Oxalis erythrorhiza* [140] and 5-heptadeca-trienylresorcinol isolated from the mushroom *Merulius incarnatus* [122] were reported to be a potent inhibitor of *Leishmania amazonensis* and *L. donovani* [140]. Similarly, 5-(11′(S)-hydroxy-8′-heptadecenyl)resorcinol and 5-(12′(S)-hydroxy-8′,14′-heptadecadienyl) resorcinol isolated from the leaves of *Stylogyne turbacensis* showed the strongest activity in the leishmania assay and only moderate activity against a drug-resistant strain of *Trypanosoma cruzi* [163]. The anacardic acids present in the petroleum ether extract of *Viola websteri* Hemsl. as well as pure compounds obtained by fractionation exhibited antiplasmodial activity against

Plasmodium falciparum [164]. Benzoquinone embelin isolated from an Argentinean collection of *Oxalis erythrorhiza* was found to be active against *Trypanosoma cruzi* [140].

Long-chain 5-*n*-alkylresorcinol homologues isolated from *Anacardium occidentale* also have molluscicidal activity against *Briomphalaria glabrata*, a parasite causing schistosomiasis, a serious tropical disease [127]. Similarly, a high activity of this homologue was also demonstrated against the *Filaria* class of worms [165]. An insecticidal activity of phenolic lipids from *Ginkgo biloba* leaves has been reported [166, 167]. It was also shown that 6-[(*Z*)-10-heptadecenyl]-2-hydroxybenzoic acid from the external seed coat of *G. biloba* has an acaricidal activity against *Panonychus citri*. The contact toxicity of this compound was similar or significantly superior to those of pyridaben and omethoate, systemic insecticidal and acaricidal compounds [168]. Phenolic lipids also exhibit larvicidal activity. This was demonstrated for cardanol, cardol from CNSL, and their products of hydrogenation against *Aedes aegypti* larvae [169] as well as for anacardic acid from *Ozoroa insignis* against *Artemia salina* larvae [170] and Colorado potato beetle larvae [171].

Phenolic lipids affect protein structure and activity

Direct resorcinolic lipid interaction with proteins was shown in experiments with monomolecular layers of these compounds [18, 50]. It was also demonstrated that the interaction of resorcinolic lipids with several proteins caused strong quenching of the intrinsic fluorescence intensity of tryptophan residues in such proteins as erythrocyte spectrin [172], the proteins of photosystems [55], and trypsin [18]. Anacardic acids from the leaves of *Gingko biloba* are able to bind to factor VIIa and prevent its binding to sTF [173].

Long-chain resorcinolic lipids caused a decrease in acetylocholinesterase activity in the erythrocyte membrane while simultaneously stimulating the activity of Ca^{2+}-dependent ATPase [174]. The inhibition of acetylcholinesterase activity in erythrocyte ghost's has also been observed for other phenolic lipids. A potent inhibitor of acetylcholinesterase activity was merulinic acid from *Merullius tremelosus* [41]. At a concentration of 30 μM of this compound, enzyme activity was completely inhibited. Phenolic lipids from CNSL showed a similarly strong effect on acetylcholinesterase activity [175]. The most active of them all was cardol, which exhibits an inhibitory activity similar to that of merulinic acid [41]. Acetycholinesterase activity was also decreased by phenolic lipids isolated from immature CNSL [76]. It has been reported that non-isoprenoid phenolic lipids of CNSL can be used as the starting material for the design of new candidates for AChE enzyme inhibitors [176].

The modulatory properties of 5-*n*-alk(en)ylresorcinols on the activity of membrane proteins may result not only from their direct interaction with a protein molecule, but also from alterations in their lateral mobilities and/or in the ability to interact with the phospholipid bilayer surface. This suggestion is supported by studies on the effect of resorcinolic lipids on fibrinogen affinity to its receptor in platelet membranes. Incubating cells with micromolar concentrations of various alkylresorcinol homologues caused a significant decrease in fibrinogen affinity to its receptor [177]. Studies on the kinetics of pancreatic phospholipase A2 hydrolysis in a phosphatidylcholine bilayer modified by alkyl(en)ylresorcinol homologues also suggest the same possibility. It was shown that 5-*n*-alkylresorcinol homologues incorporated into liposomal membranes caused a drastic increase in the latency phase of the enzyme [178]. This depended on the chemical structure of tested phenolic lipid molecules. 1-sulfate-3-myristoyl-5-pentadecylbenzene present in the lecithin liposomal bilayers caused a drastic decrease in the first phase of the cobra venom phospholipase A2 kinetic curve (called the "lag time"), which suggests that this compound can cause defects in phospholipid packing within the bilayer [23]. A strong inhibitory activity was observed for cobra venom, phospholipase A2, in the presence of a mixture of bacterial alkylresorcinols in lecithin black lipid membrane and phospholipid emulsion systems. Almost complete inhibition (95%) of the studied enzyme was observed [32].

Panosialins, compounds with antibiotic properties isolated from the fungus *Streptomyces*, inhibited the activities of several types of enzymes, such as salidases PR8, HVJ, acid phosphatases, polygalactouronase, and α1,3-fucosyltransferase [179–181].

It was shown that 3-phosphoglycerate dehydrogenase, a key enzyme of triglyceride synthesis in adipocytes, was efficiently inhibited by 5-*n*-pentadecyl and 5-*n*-isopentadecylresorcinol from *Streptomyces* [182] as well as by higher alkylresorcinol homologues isolated from a cereal bran milling fraction [183, 184]. Further in vitro studies showed that these compounds also prevent triglyceride accumulation in 3T3-L1 cells [184].

Inhibition of 3-phosphoglycerate dehydrogenase was also demonstrated for anacardic acids [185, 186]. Anacardic acid also exhibited an ability to inhibit the growth and lipid synthesis of *Bacillus subtilis* and *Lipomyces starkeyi* [186]. Glyceraldehyde-3-phosphate dehydrogenase is an attractive target for the development of novel chemotherapeutic agents for the treatment of Chagas' disease, caused by the flagellate protozoan *Trypanosoma cruzi*. Natural and synthetic anacardic acid derivatives were found to be potent inhibitors of the target enzyme. A detailed mechanistic characterization of this effect showed noncompetitive inhibition with respect

to both substrate and cofactor [187, 188]. C15 5-*n*-alk(en)-ylresorcinols and alkylphenols from *Ginkgo biloba* exhibited inhibitory properties against other dehydrogenase enzymes, such as glucose-6-phosphate dehydrogenase, lactate dehydrogenase, isocitrate dehydrogenase [189], and phosphatase [110].

Histone acetyltransferases are a group of enzymes that covalently modify the N-terminal lysine residues of histones by the addition of acetyl groups from acetyl-CoA. Dysfunction of these enzymes is often associated with the manifestations of several diseases, primarily cancer. Attenuation of histone acetyltransferase activity can be a good method to understand the role of this enzyme in cell metabolism. Inhibition of cellular histone acetyltranferase activity by anacardic acid will lead to decreased histone acetylation, a more compacted chromatin structure, and reduced transcriptional activity. It was proposed that anacardic acids, which have structural similarities to acetyl-CoA (the acetyl donor for histone acetyltransferases), may inhibit the binding of acetyl-CoA to the active site of these enzymes [190]. Anacardic acids inhibited p300 and p300/CBP-associated factor histone acetyltranferase activities [191] and the Tip60-dependent acetylation and activation of the ATM protein kinase in HeLa cells and sensitized the cells to the cytotoxic effects of radiation. The ability of anacardic acid to inhibit Tip60 signaling pathways in vivo demonstrates that it can cross the cell membrane [190]. Starting from anacardic acids, a series of 28 analogues were synthesized and investigated for histone acetyltranferase-inhibitory properties and effects on cancer cell growth. The compounds inhibited up to 95% of histone acetyltranferase activity in vitro, and there was a clear correlation between their inhibitory potency and cytotoxicity towards a broad panel of cancer cells. Interestingly, all the tested compounds were relatively nontoxic to nonmalignant human cell lines [192]. Similarly, a group of benzamides related to anacardic acid amide with alkyl chains of defined length exhibited activities similar to those of anacardic acids, as they behaved as human p300 inhibitors and induced a decrease in histone acetylation levels in immortalized HEK cells [193]. Pentadecylidenemalonate, a simplified analogue of anacardic acid, was identified as the first mixed activator/inhibitor of histone acetyltransferases [194]. Histone acetylation also seems to be important for the regulation of proinflammatory gene expression in *Legionella pneumophila*-infected lung epithelial cells. *L. pneumophila* strain 130b induced the expression of the important chemoattractant IL-8. This process was decreased by the histone acetyltransferase inhibitor anacardic acid [195]. Anacardic acids reversibly and noncompetitively inhibited the histone acetyltransferase activity of recombinant PfGCN5 in parasite nuclear extracts [196].

Phenolic lipids from cashew were also found to be inhibitors of several enzymes. This was shown for α-glucosidase, invertase and aldolase [197], tyrosinase [198], urease [136], and Aurora kinases [199]. Binding assays with a fluorescently labeled probe showed that ginkgolic acid and anacardic acid inhibit protein SUMOylation both in vitro and in vivo without affecting in vivo ubiquitination [200].

Alkyl hydroxybenzenes are capable of stabilizing enzymes in aqueous media and increasing their catalytic activity. They have a chemical chaperon function as ligands that nonspecifically interact with biopolymer molecules, change their conformation, and increase their resistance to denaturing factors [201]. C7- and C12-alkylhydroxybenzene affected both the degree of protein swelling, viscosity, and the degree of hydrophobicity. The effects depended on the structure of these compounds, their concentration, and the pH of the solution [202].

Anacardic acids isolated from *Schoepfia californica* were found to be DNA polymerase β inhibitors and compounds that potentiate the action of DNA-damaging agents such as bleomycin [101, 203, 204].

Conclusions

Phenolic lipids, compounds which have been known for a century, are more recently being extensively studied not only from the biological but also from the chemical point of view. It is now known that they can be used as starting materials in the semisynthesis of compounds for various biological activities; therefore, the biological and biochemical effects and the chemistry of these compounds should be very closely interrelated. Until now, most of the observed activities of phenolic lipids were rather nonspecific and resulted from their amphiphilic and phenolic nature. Further investigation on various aspects of biology may open new opportunities to exploit their properties, as, for example, chemopreventive and antitumor agents, and to develop pharmaceuticals based on phenolic lipid constituents.

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