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Review

Synthesis and biological activity of polyprenols

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ABSTRACT

The polyprenols and their derivatives are highlighted in this study. These lipid linear polymers of isoprenoid residues are widespread in nature from bacteria to human cells. This review primarily presents the synthesis and biological activities of polyprenyl derivatives. Attention is focused on the synthesis and biological activity of dolichols, polyprenyl ester derivatives and polyprenyl amines. Other polyprenyl derivatives, such as oxides of polyprenols, aromatic polyprenols, polyprenyl bromide and polyprenyl sulphates, are mentioned. It is noted that polyprenyl phosphates and polyprenyl-linked glycosylation have better antibacterial, gene therapy and immunomodulating performance, whereas polyprenyl amines have better for antibacterial and antithrombotic activity. Dolichols, polyprenyl acetic esters, polyprenyl phosphates and polyprenyl-linked glycosylation have pharmacological anti-tumour effects. Finally, the postulated prospect of polyprenols and their derivatives are discussed. Further in vivo studies on the above derivatives are needed. The compatibility of polyprenols and their derivatives with other drugs should be studied, and new preparations of polyprenyl derivatives, such as hydrogel glue and release-controlled drugs, are suggested for future research and development.

Contents

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1. Introduction

Polyprenols are lipid linear polymers composed of several isoprenoid units (as shown in Fig. 1a); they are widespread in nature from bacteria to plants, such as mammals, yeast, plants, bacteria and fungi [1]. The search for polyprenols was initiated by the accidental discovery of solanesol as a ubiquinone-accompanying lipid in tobacco leaves [2]. when Rowland RL et al. extracted flue-cured tobacco with methanol and ether. The isolation of polyprenols was first achieved from a contaminant of cellulose pulp in a paper plant [3]. The only difference in structure between polyprenols and dolichols is the hydrogenation of the double bond in the α-residue (as shown in Fig. 1), while the latter substance mainly participates in the metabolism of living cells and plays an important role in the structure and function of biofilms [4–7]. Polyprenols in cells are generally in the form of free alcohols, carboxylic esters and phosphate esters. They have species specificity [8]. and their degree of polymerization and content varies by plant species, tree age, parts of the plant [9–11] and even seasons, as shown in Table 1.

Polyprenols have non-toxic, non-mutagenic, non-teratogenic and non-carcinogenic effects in humans. In addition, their biological activities have significant anti-tumour, anti-hepatitis C virus and anti-HIV effects and are adjuvants for chemotherapy for leukaemia and radiotherapy [26–28]. Polyprenols can also remedy hypertension, high cholesterol, diabetes, gout, lupus and other immune function disorders [29–32]. Hence, increasing focus has been placed on the research and development of polyprenols.

Polyprenyl compounds in vivo are closely related to the stability of membranes and the formation of sugar chains. Polyprenols are also interesting because of their important role as lipophilic sugar transporters in the biosynthesis of bacterial polysaccharides and glycoproteins. The physiological function of endogenous polyprenols of plants is not yet fully elucidated although it is known that they open Ca^{2+} channels of bilayer membranes and enhance the biosynthesis of nuclear protein. Therefore, the modification is usually carried out in order to establish the structure or to study polyprenyl derivatives as potential biologically active substances. Research shows that the hydroxyl group in α-residue of polyprenols is substituted by different groups, although there are significant differences in bioactivity. Hence, polyprenols and their derivatives are demonstrated to have a wide range of pharmacological effects, such as anti-tumour and anti-anaemia effects, and are developed as psychosis drugs [14].

In recent years, the extraction, purification [16,33–36], synthesis [37–40], structure and function [41–43], biological activity [44–47], and pharmacology of polyprenols and their derivatives have been studied. [48,49]. However, the review of their derivatives has rarely been reported. This review focuses on the synthesis and biological activity of polyprenyl derivatives. Our aim is to provide a reference and summary for current and future researchers.

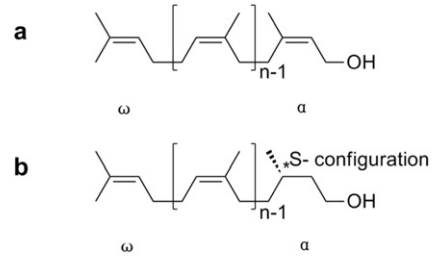


Fig. 1. The structure of polyprenols and dolichols.

2. Polyprenyls

2.1. Isolation and analysis of polyprenyls

Polyprenyls are isolated from the neutral part of plant extracts. However, optimal conditions are developed for each specimen based on plant composition [16]. The separation and purification process of polyprenyls is roughly as follows [50]:

Plants contained PPs $\xrightarrow{a,b}$ $\xrightarrow{c}$ $\xrightarrow{d}$ $\xrightarrow{e}$ purified PPs.

Methods and reagents: a. solvent extraction, ethanol, petroleum ether or other solvents; b. hydrolysis; c. molecularly distilled; d. decolouration; e. column chromatography or HPLC.

Polyprenols can then be analysed or modified for further applications. However, their low content in plants, low yield through purification and high cost prevent polyprenyls from being fully utilized industrially. Extensive studies have focused on the detection of polyprenols from gymnosperms and angiosperms. Thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) have been used to analyse these substances. Recently, supercritical fluid chromatography (SFC), high-performance liquid chromatography/mass spectrometry (HPLC/MS) and pyrolysis–gas chromatography/mass spectrometry (PY–GC/MS) have also been used [20]. Furthermore, atmospheric

Table 1
Distribution of polyprenols in different plants.

The sources of PP	Degree of polymerization (n)	Content/%	Reference
Tobacco leaves	9	0.3–3	[12]
Cotton leaves	10–12	1.8–2.5	[13,14]
Lentinus edodes (Shiitake)	6–9	0.002	[15]
Mallotus japonicus	9–11	0.002–0.2	[16]
European fir	14–16	0.46–1.25	[16]
Potentilla aurea	18–42 (20–28)	0.5–1	[16]
Mulberry leaves	9–12	0.13–3.93	[17]
Cupania latifolia	6	0.031	[18]
Althaea officinalis	9–13	0.35–1.37	[19]
Ginkgo biloba Leaves	14–24	1.0–1.96	[20,21]
Coccinia grandis (L.)	12	0.008	[22]
Soybean leaves (wet)	10–12	0.1–0.2	[23]
Rubber old leaves	12–23	0.45	[24]
Rubber flowers	16–24	0.099	[24]
Taxus chinensis var. mairei	14–24	~3	[25]

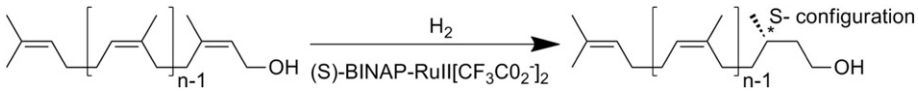


Fig. 2. The scheme of S-dolichol through asymmetric hydrogenation.

pressure photoionization (APPI) is an appropriate method for the identification of dolichols, polyprenols and their esters in natural samples [47].

2.2. Application of polyprenyls

The existence of life requires polyprenols. For instance, polyprenols from Ginkgo biloba L. leaves are generally composed of 15 to 21 isoprene units [21] and are the most closely related to dolichols in structure, so they can be studied as patterns of dolichols or even be considered to replace dolichols for human's life. Solanesol has been used for the synthesis of CoQ10 and vitamin K_2 [51], because its structure is *trans*-type and it is present in very large amounts in tobacco leaves and other solanaceous plants.

Currently, companies such as Larodan Fine Chemicals AB in Sweden and Indofine Chemical Company, Inc. in the United States produce small quantities of polyprenols for scientific research purposes. A Russian company by the name of SibEX has developed the world's first commercial polyprenols manufacturing facility in the university city of Tomsk in central Siberia. SibEX claims the ability to manufacture polyprenols at up to 20 kg per month from conifer needles sourced from Siberian forests. SibEX is majority-owned by Solagran, which has developed a medicinal product by the name of Ropren, the main substance of which is a 95% purity concentrate of polyprenols. It was demonstrated previously that Ropren exhibits immunomodulatory properties and stimulates humoral response of the organism to phagocytosis, which may be successfully used for treating various infectious, allergic and autoimmune diseases. In addition, there are grounds to assume that Ropren displays certain cerebroprotective and hepatoprotective effects [52]. Fedotova et al. [53] reported that Ropren ameliorates cognitive and behavioural deficiencies in an animal model relevant to Alzheimer's disease, according to Hooff [54], and it was administered at a dose of 8.6 mg/kg for 28 days, per os, to rats with β-amyloid peptide-(25–35)-induced amnesia. Ropren has recently been registered as a pharmaceutical in Russia and has recently commenced being used in Russian hospitals for the treatment of liver diseases and related conditions.

3. The synthesis of polyprenyl derivatives and their biological activities

3.1. Dolichols

Dolichols have an *E*, *E*-farnesyl residue at the ω-residue of their prenyl chains, but they are different from other polyprenols because the α-residue is saturated. Dolichols are important physiological compounds in the human body for regulating the stability and permeability of membranes. Dolichol phosphates are a kind of glycosyl carrier and essential component for human glycoprotein biosynthesis [55–57]. The exogenous dolichols are mainly derived from the liver, kidney, pancreas, spleen, thyroid and other organs in mammals. However, their content is very low and is generally three ten thousandths of the wet weight of the organs [58,59]. Their extraction, isolation and purification are tedious. These reasons have led to their rarity and further limit the development of dolichol derivatives and drugs.

In the early 1980s, Suzuki found that the structure of *S*-dolichols in mammals is similar to polyprenols. Hence, polyprenols have been the best semisynthetic raw materials of *S*-dolichols and their derivatives [60–62]. Polyprenols can also be used directly as research model alternatives of *S*-dolichols [63,64]. The best recognized example of *all-trans* alcohol is solanesol (*all-trans* Prenyl-9, i.e., there are nine isoprene units in the molecule) occurring in solanaceae plants and spadicol (*all-trans* Prenyl-10) isolated from the spadix of Arum maculatum [16]. Welti [65] emphasized that the disorder of dolichol biosynthesis and their respective symptoms were caused by MVA and HIDs virus, whereas others were due to congenital disorders of glycosylation (CDG). Therefore, exogenous dolichols are mainly used for immunomodulating, CDG and gene therapy. In addition, other biological activities have been reported in other references, such as free radical scavenging [66], anti-tumour, antibacterial, and antithrombotic effects, and hepatic protection [11,67,68].

3.1.1. Catalytic hydrogenation

Mankowski found that the α-terminal of Prenyl-11 was hydrogenated more easily. He obtained Dolichol-11 (i.e., eleven isoprene units in the molecule) by catalytic hydrogenation, and the yield was 60% [69]. This method has been quoted in many subsequent studies [70–72], where the number of isoprene units of polyprenols ranged from 6 to 25. However, this selective α-terminal oxidation was not stereospecific because it could also form *R*-configuration dolichols. On the other hand, separating *S*-dolichols from the reaction products requires not only more complex column chromatographic techniques but also a larger workload [73].

3.1.2. Grignard reaction

Takigawa [74] prepared *S*-dolichols with the Grignard reagent using the copper complex Li_2CuCl_4 as catalyst and polyprenyl acetate as the raw material.

Bizzarri [75] obtained (*R*)-4-benzyloxy-2-methyl-1-butanol, which is a high-purity and stereospecific product, and then formed chiral

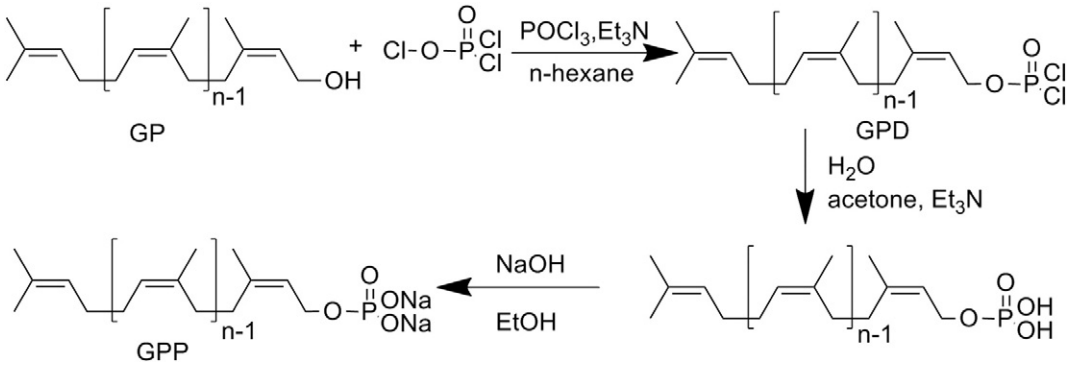
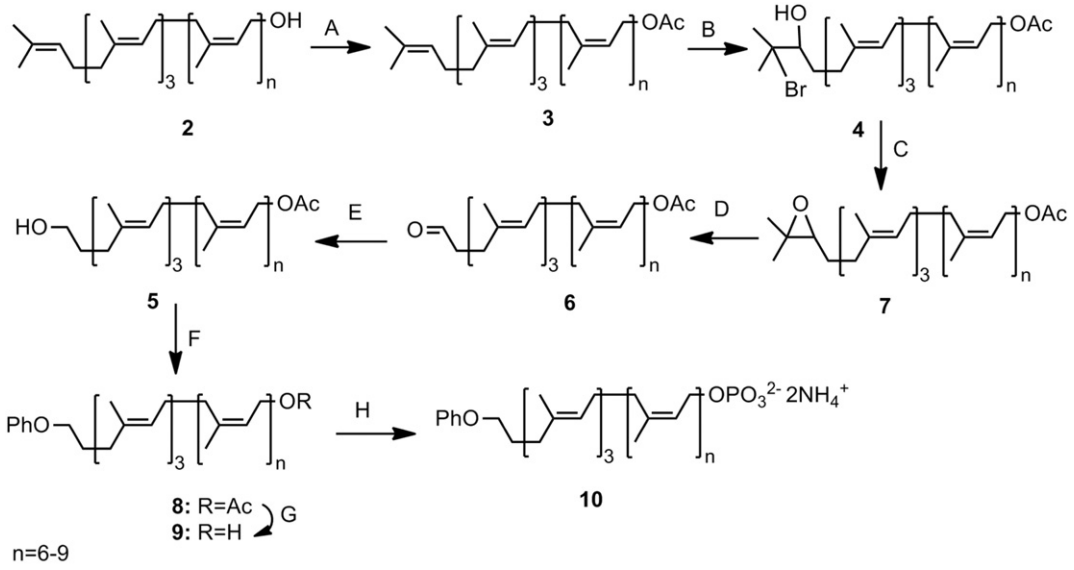


Fig. 3. The scheme of polyprenyl dichlorophosphite and polyprenyl phosphate disodium.



Reagents and conditions: A. Ac_2O, Py(Pyridine), 20℃, (~100%); B. NBS, aq. THF(Tetrahydrofuran), 20℃ (55%); C. K_2CO_3, PhH-MeOH, 20℃ (62%); D. $HIO_4{\cdot}2H_2O$, Et_2O-THF, 20℃ (98%); E. $NaBH_4$, DME(Dimethyl ether), 20℃ (60%); F. PhOH, DEAD(Diethylazodicarboxylate), Ph_3P, THF, 0→20℃ (44%); G. K_2CO_3, 20℃ (66%);H. 1)CCl_3CN, $Bu_4NH_2PO_4$, CH_2Cl_2, 20℃, 2) Dowex 50W×8 (NH_4^+),Bu^{t}OMe-MeOH, 3) chromatography on DEAE-cellulose DE-52(OAc^-), NH_4OAc in MeOH (49%)

Fig. 4. The scheme of bacterial undecaprenyl phosphate.

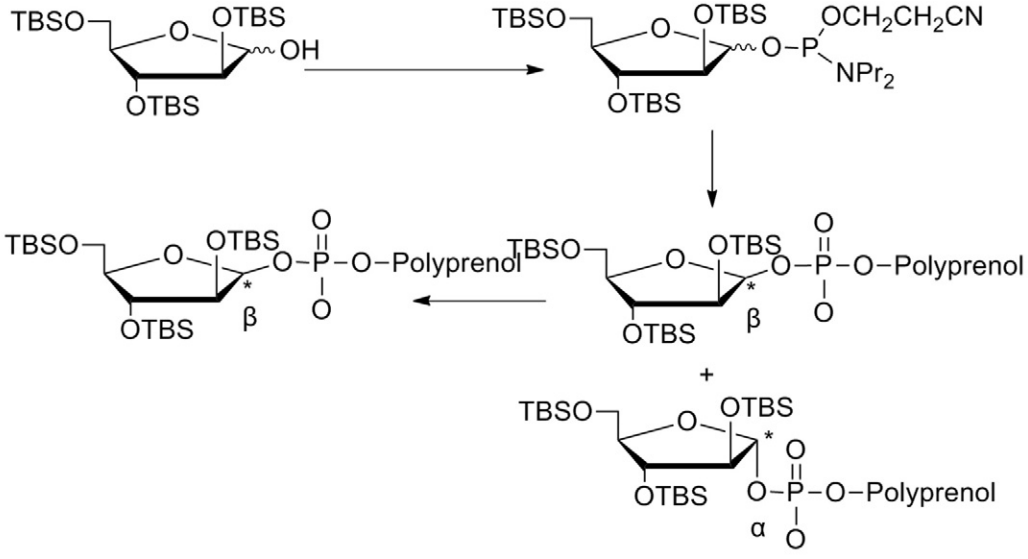
C5 synthon as a Grignard reagent by bromination, to finally form *S*-dolichols.

3.1.3. Asymmetric hydrogenation

Imperiali [76] used a divalent ruthenium complex (*S*)-BINAP-Ru-$^{II}[CF_3CO_2^-]_2$ as a catalyst for the selective hydrogenation reaction to obtain *S*-dolichols (as shown in Fig. 2). The reaction conditions were as follows: the pressure was 10.34 MPa; the ratio of polyprenol to catalyst was 100:1 (*w*/*w*); the temperature was 25 °C; the concentration of polyprenol in CH_2Cl_2–MeOH (2:1) solution was 0.35 mol/L; and the reaction time was 24 h. This reaction was highly chemoselective because more than 95% *S*-dolichols was formed, as measured by optical activity.

3.1.4. Polyprenol reductase synthesis

Gründahl [77] focused on a 6-year-old patient with a new type of CDG-I caused by a defect of the steroid 5α reductase type 3 gene (SRD5A3). This gene was recently identified to encode the polyprenol reductase. This study emphasized the possibility of an alternative



(i) 2-cyanoethyl N, N-diisopropylchlorophospsorylamidite, $EtNiPr_2$, CH_2Cl_2, -78°C; (ii) a: Polyprenol, tetrazole (b): H_2O_2, THF (c): KOH, MeOH (d): separate SiO_2; (iii) NH_4OH, MeOH

Fig. 5. The scheme of β-D-arabinofuranosyl-1-monophosphoryl polyprenols.

dolichols pathway, which was demonstrated by normal dolichol levels in the described patient.

3.2. Polyprenyl ester derivatives

3.2.1. Polyprenyl acetic ester

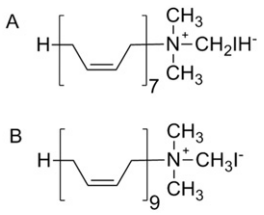
There are different forms of polyprenols in different plants, e.g., some polyprenols exist in the alcoholic form in Kashiwaba, pine needles and Potentilla discolour, whereas others are in the form of acetic esters in Ginkgo biloba leaves, birch and yeast [78–80]. Prenylacetic esters possess distinct anti-ulcer and antithrombotic activities without harmful side effects [53,62].

Khidyrova [81] modified polyprenols from cotton leaves by acylation with monobasic acid anhydrides, and the yield of polyprenyl acetic ester was 69%. Tao et al. [82] synthesized polyprenyl acetate (GPA) by esterification with acetic anhydride and polyprenols in Ginkgo biloba leaves with ayield of 91%. The result showed that GPA demonstrated bacteriostasis, and there was no synergy on Staphylococcus aureus and Bacillus subtilis between polyprenols and GPA. Veselovsky et al. [17] reported a simple method for the preparation of polyprenyl acetates (yield of 100%) using Ac_2O and Py in tetrahydrofuran (THF, 20 min at 20 °C).

Zhou et al. [83] prepared polyprenyl acetate in an ice bath with Ginkgo biloba polyprenols and acetic acid. They also measured the bacteriostasis of the acetate, suggesting that the antibacterial activity of polyprenyl acetate on Staphylococcus aureus and Escherichia coli was better than polyprenols, and the antibacterial activity on Staphylococcus aureus was superior to other bacteria, such as E. coli, Bacillus subtilis and Salmonella. Moreover, there was minimal activity toward Aspergillus niger and yeast.

3.2.2. Polyprenyl phosphates

Polyprenyl phosphates and dolichyl phosphates are found in the cell membrane as carriers of glycosyl residues [84,85]. The dolichol phosphate cycle plays a major role in the synthesis of glycoproteins, it facilitates the process of cellular membrane glycosylation, that is, the synthesis of glycoproteins that control the interactions of cells, support the immune system and the stabilization of protein molecules. The biological activities of polyprenyl phosphates have been reported, including antibacterial and anti-tumour activities [82,86]. For instance, Kuznecovs et al. [45] found that polyprenol in concentration 10^{-3} – 10^{-4} M induced apoptosis in MCF-7 cells within 3 – 4 h. Moreover, they can also be used as dolichol models and are promising candidates for use in gene therapy and immunomodulation [87,88]. A well-documented function of polyprenol diphosphates is their role as cofactors of protein glycosylation in eukaryotes [89,90]. Janas [91] reported that a lengthy polyprenol chain was beneficial for lipid acceptors, and this was related to their ability to fluidize the membrane bilayer. Rasadkina et al. [92] obtained di- and mono-amidophosphites and thiophosphates of polyprenols by phosphorylation of the hydroxyl group of polyprenols with the purpose of producing novel bioactive compounds.



Therein, **A** is the structure of heptaprenyl-trimethylammonium salt and **B** is that of nonaprenyl-trimethylammonium salt, respectively

Fig. 6. Structures of heptaprenyl-trimethylammonium (A) and nonaprenyltrimethylammonium (B) iodides.

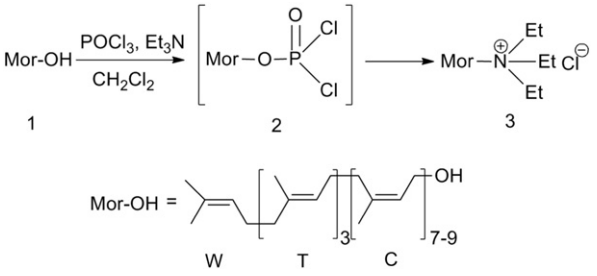


Fig. 7. The scheme of triethylmoraprenylammonium chloride.

Wang et al. [93] synthesized two Ginkgo biloba polyprenyl phosphates (as shown in Fig. 3), including polyprenyl dichlorophosphite (GPD) and polyprenyl phosphate disodium salts (GPP). They also investigated the antibacterial activities and antioxidant properties toward five bacteria (Salmonella, *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis*). The antibacterial activities of polyprenyl phosphates were better than the other ingredients from *Ginkgo biloba* leaves. Additionally, the synergy was the strongest for anti-salmonella between polyprenols from *Ginkgo biloba* and GPP when their mass ratio was 62.59%:37.41%.

Veselovsky et al. [17] prepared a biologically active analogue of bacterial undecaprenyl phosphate bearing a phenoxy group at the ω-terminal of the chain. As shown in Fig. 4, it included the selective van Tamelen epoxidation of the ω-terminal isoprene unit of polyprenyl acetates, conversion of the epoxides into ω-terminal aldehydes, their hydride reduction into hydroxy acetates, followed by the Mitsunobu condensation with phenol, and phosphorylation of the resulting phenoxy alcohols. The biological activity of the obtained phosphates was tested by the radiometry method. The result showed that the products were improved by 50% and 66% for the enzymes from S. arizonae and A. hydrophila AH-1, respectively, compared to moraprenyl diphosphate α-D-glucose prepared previously [94].

3.2.3. Polyprenol-linked glycosylation

Polyprenol-linked glycosylation is important for the treatment of CDGs, immunomodulation, and antibacterial and anti-tumour activity

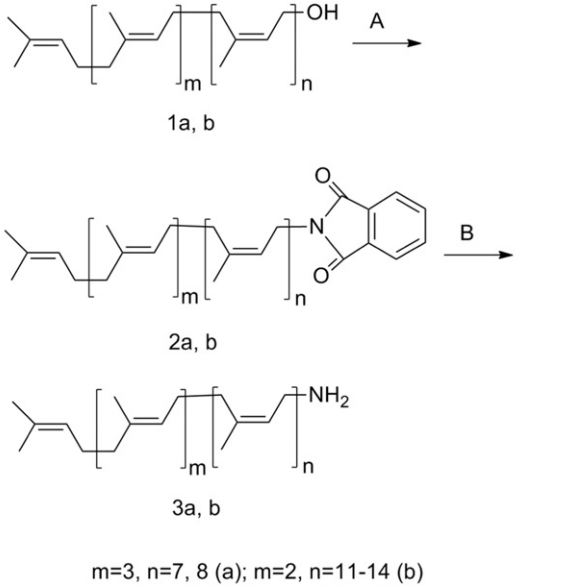


Fig. 8. The scheme of polyprenylamines.

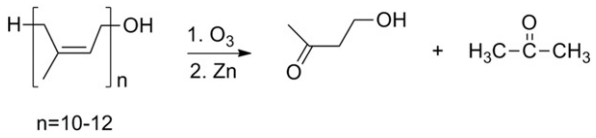


Fig. 9. The route of ozonolysis of polyprenols.

[33,65]. Lee et al. [95,96] synthesized a series of β-D-arabinofuranosyl-1-monophosphoryl polyprenols (as shown in Fig. 5) with polyprenols isolated from *Fica elastica* and polysaccharides (arabinogalactan (AG) and arabinomannan (AM)). The results showed that product 1 (the α-anomer) was inactive as a donor, whereas the β-anomers were assayed only for arabinosyl transferase activity. In this context, it was evident that the long chain polyprenol derivatives C_{50} (the number of isoprene units in the polyprenol derivatives was 10, i.e., n = 10), C_{55} (n = 11) and dolichol C_{55} (n = 11) were active within this mycobacterial arabinosyl transferase assay as sugar donors. The high transferase activity associated with the dolichol derivative (Dolichol-11) was in accord with other bacterial activities. A variety of polyprenyl donors has been studied extensively [97], particularly the O-antigen biosynthesis in *Salmonella anatum*, where the polyprenyl donors showed a lake of specificity for the saturation state of the first isoprene unit.

Hartley et al. [98] reported that long-chain polyprenyl phosphates were used as facilitators of glycan assembly in essential bioprocesses. Moreover, N-linked protein glycosylation and peptidoglycan biosynthesis have been extensively studied. Some researchers have also explored the reasons why unmodified polyprenols were evolutionarily conserved and why polyprenyl phosphates are universally and specifically utilized for membrane-bound glycan assembly [99,100].

3.3. Polyprenylamines

3.3.1. Quaternary polyprenyl ammonium salts

Madeja et al. [101] prepared analogue cationic linear poly-*cis*-isoprenoid with natural plant polyprenol in a mixture and dioleyl phosphatidylethanolamine (as shown in Fig. 6). This cation was an effective lipofection agent for eukaryotic cells. The lipofecting activity of heptaprenyl-trimethylammonium salt was better than that of the nonaprenyl-trimethylammonium salt due not only to the length of the isoprenoid chain of the nonaprenyl radical, as postulated by Tarahovsky et al. [102] but also to the *all-trans* structure of the isoprenoid unit.

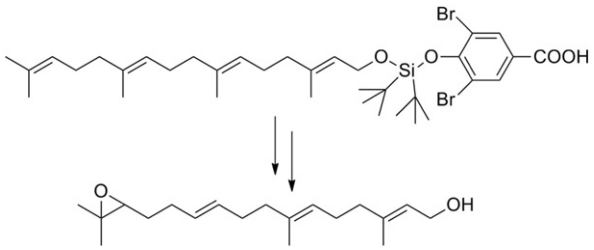


Fig. 11. The scheme of epoxidation of polyolefinic polyprenols.

Sizova [103,104] et al. developed a one-pot procedure for the synthesis of quaternary polyprenyl-ammonium chloride with a good yield (72%) and high *cis*-stereoselectivity on the α-terminal isoprene unit of polyprenol. This compound can be regarded as an example of a new class of cationic lipids (as shown in Fig. 7). This procedure opened a new method for the synthesis of cationic lipids, which are useful as antivirotics and are potential transfection mediators.

Gawarecka et al. [105,106] determined the ability of polyprenyl derivatives to affect the bilayer properties. For this purpose, they used DPH anisotropy to measure liposomes containing polyprenols or their cationic form. In parallel experiments, the effect of polyprenyl derivatives on the properties of model membranes made from POPC, PSM and cholesterol was elucidated. To observe the effects of polyprenols on the formation of ordered domains containing sterols, the steady state quenching of CTL by quencher 7SLPC was measured. Their experiments indicated that *trans*-prenols and their cationic derivatives increased the order of lipids in the liposomal structure. On the other hand, long chain polyprenol lipids had an affinity for cholesterol-rich microdomains ('rafts') and appeared to affect their biophysical properties. Utkina et al. [107] studied the quaternization of triethylamine, 4-dimethylaminopyridine, and N-methylimidazole to develop a versatile method for the preparation of quaternary salts containing a moraprenyl substituent.

3.3.2. Polyprenylamines

Veselovsky et al. [108] developed a facile route to synthesize polyprenylamines based on relatively accessible plant polyprenols. The reaction conditions are shown in Fig. 8. They studied the pharmacological properties of these compounds, such as the immunomodulating, antiulcer, and antithrombotic activities, which were also discussed previously for the amino derivatives of linear isoprenoids [109,110]. Furthermore, polyprenyl amines exhibited antithrombotic activity and

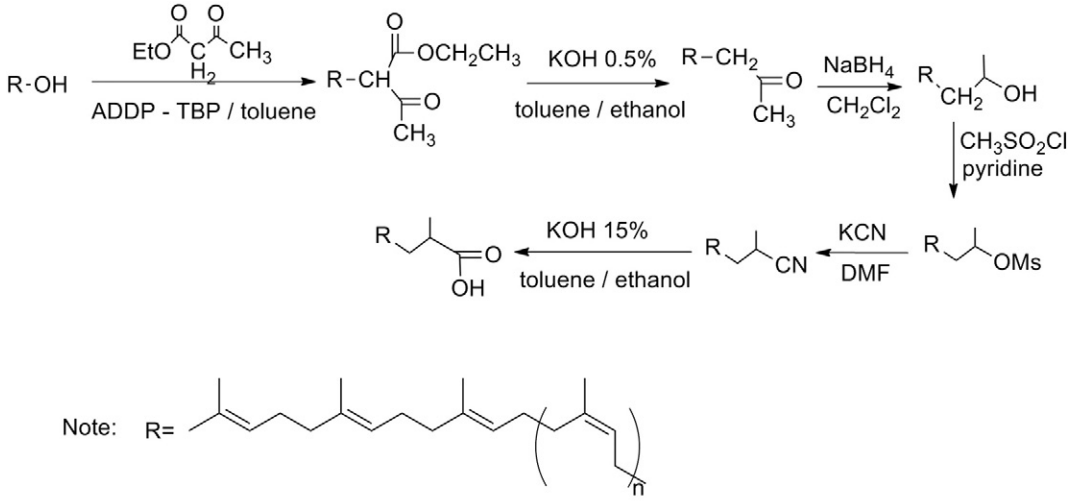


Fig. 10. The scheme of nordolichoic acid.

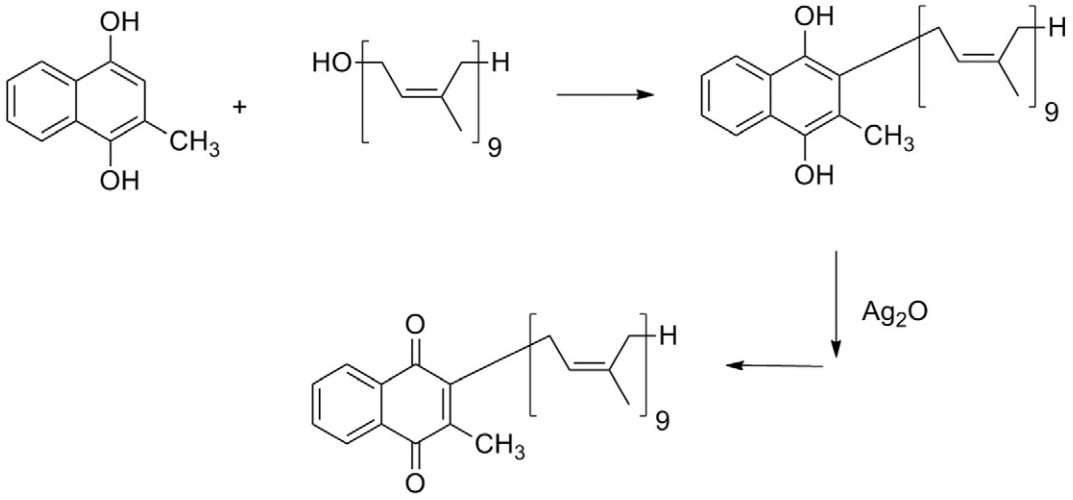


Fig. 12. The scheme of analogues of vitamin K_2.

could be used for the prophylaxis and treatment of cardiac stenosis, chronic atherosclerosis, and brain thrombosis [111].

3.4. Oxides of polyprenols

Oxidative transformations involving the hydroxyls and ω-methyls of polyprenols were used to produce α, ω-Dolichols, diesters, aldehydoalcohols and hydroxyacids [112]. These polyprenyl derivative products (including 7–9 isoprene units in their chain, i.e., n = 7–9) were analysed for potential anti-inflammatory, antiulcer, hepatoprotective and cardio-active activity [113].

3.4.1. Polyprenyl aldehydes

Acetates of castoprenols were isolated and oxidized with MnO_2 to synthesize the corresponding aldehydes [16].

$$\text{H-(CH}_2\text{-CMe = CH-CH}_2)_n\text{-OH} \longrightarrow \underset{n=11-13}{\text{H-(CH}_2\text{-CMe = CH-CH}_2)_{n-1}\text{-CH}_2\text{-CMe = CH-CHO}}$$

Ozonolysis of malloprenol occurred in ethylacetate at −70 °C to form the ozonide and was then reduced by powdered zinc to obtain levulinic aldehyde and acetone (as shown in Fig. 9) [114]. Kryshtal [115] developed novel methods to catalyse saturated and unsaturated aldehydoesters. The results of the synthesized compounds in in vitro assays were compared with the known data on their pharmacological effects in vivo.

3.4.2. Nordolichoic acid

Houte et al. [70] described the synthesis of nordolichoic acid and [1-^{14}C] nordolichoic acid with polyprenol isolated from the leaves of Ginkgo biloba (as shown in Fig. 10). Polyprenol was coupled with ethyl acetoacetate and 1,1-(azodicarbonyl) dipiperidine/tributylphosphine, followed by hydrolysis, decarboxylation and reduction. Firstly, the 2-polyprenyl-1-methylethanol was yielded. This alcohol was converted into a mesylate, was subjected to one-carbon elongation with KCN and was finally converted to the acid by hydrolysis of the nitrile.

3.4.3. Position-selective epoxide of polyprenols

According to an internal control element for intramolecular reaction, an effective strategy of the efficient site-selective epoxidation of poylolefinic isoprenoid alcohols was developed (as shown in Fig. 11) [116]. The internal epoxidation could be directed at the double bond of the polyprenol, which were either four or five steps away from the ω-terminal of the polyprenol substrates.

3.5. Other derivatives of polyprenols

3.5.1. Aromatic polyprenols

Solanesol and 2-methyl-1,4-naphthohydroquinone were condensed by some researchers [117] and were then oxidated for analogues of vitamin K_2 (as shown in Fig. 12); these analogues were antithrombotic.

Khidyrova et al. [118] alkylated *o*-cresol using polyprenols in the presence of aluminium cresolate. The content of the *o*-polyprenylcresols products reached 41% and 11% of the *p*-substituted isomers.

Li et al. [119] provided strong support for a pathway for the progressive aromatization of polyprenols. These compounds are specific markers for the Ostracode Zone sourced oils in the Lower Mannville Group reservoirs in southern Alberta and may serve as excellent oil-source correlation parameters.

3.5.2. Polyprenyl bromide

Utkina et al. [120] developed an efficient method for the synthesis of moraprenyl bromide (~100%) by the reaction of moraprenol

Table 2
Biological activities of polyprenol and polyprenyl derivatives.

	Antibacterial	Antitumor	Antiulcer	CDG	Gene therapy	Immunomodulating	Antithrombotic	Hepatic protectors
Dolichols	*	**	*	**	**	**	*	*
Polyprenyl acetic esters	*	*	**	*			*	
Polyprenyl phosphates	**	*	*	**	**	**	*	*
Polyprenyl-linked glycosylation	**	*		**	**	**		
Polyprenyl amines	**		*		*	*	**	*
Oxide of Polyprenols	*							*
Aromatic polyprenols							*	
Polyprenyl Sulphates					*	*		*

Note: "*" is only denotes the biological activities was reported in references; "**" is referred to a better biological activity.

(Prenyl-13–15) with bromotrimethylsilane, and the polyprenol was extracted from the mulberry tree *Morus alba* leaves.

3.5.3. Polyprenyl sulphates

Maltsev et al. [121] synthesized dolichyl and polyprenyl sulphates as analogues of dolichyl and polyprenyl phosphates by the interaction of dolichols and polyprenols with the pyridine-sulphuric anhydride complex. The preliminary data of the biological tests of dolichyl sulphate (Prenyl-14 – 17) showed that these compounds cannot replace dolichyl phosphate in glycosylation reactions catalysed by the enzymes from rat liver microsomes, and they only slightly inhibited these reactions. On the other hand, it was also reported in the research of Yamauchi et al. that polyprenyl sulphates had antibacterial activity [109].

3.6. The comparison of biological activities of polyprenyl derivatives

Recent studies showed that polyprenols, especially the betulin type (such as ginkgo leaves polyprenols), not only had pharmacological effects (as shown in Table 2) but was were also also non-toxic to humans ($LD_{50} > 100\ g\ g \cdot kg^{-1}$) [122]. Polyprenol preparations have been performed in Latvia, Russia, Japan and other countries [123,124], and they have been used in clinical studies, supporting the further development of polyprenols and their derivatives or other polyprenol preparations.

The biological activities of polyprenols and their derivatives shown in Table 2 were summarized from the references reported herein. It is noted that polyprenyl phosphates and polyprenyl-linked glycosylation result in better antibacterial, gene therapy and immunomodulating performance; polyprenyl amines have better antibacterial and antithrombotic activity. Dolichols, polyprenyl acetic esters, polyprenyl phosphates and polyprenyl-linked glycosylation have anti-tumour effects; oxides of polyprenols have antibacterial activity and are hepatic protectors; aromatic polyprenols have antithrombotic effects; and polyprenyl sulphates can be used for gene therapy, immunomodulation and as hepatic protectors.

4. Concluding remarks

This review examines the synthesis and biological activities of polyprenols and their derivatives. Polyprenols and their derivatives are highly bioactive compounds. Their chemical and biological characteristics in vitro have been investigated, but in vivo tests are less common in the literature.

The authors hope that this review will help to attract the attention of chemists, medical researchers and biologists for a more intensive and thorough investigation of these compounds. The following aspects could be considered: (1) the tests of the derivatives in vivo; (2) the compatibility of polyprenols and their derivatives with other drugs, as suggested by Guo et al. [125]; and (3) the research and development of polyprenols and their derivative preparations, such as hydrogel glue [27] and controlled drug release.

Conflict of interest

The authors declare no conflict of interest.

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