NATURAL COMPOUNDS WITH ANTIATHEROSCLEROTIC PROPERTIES

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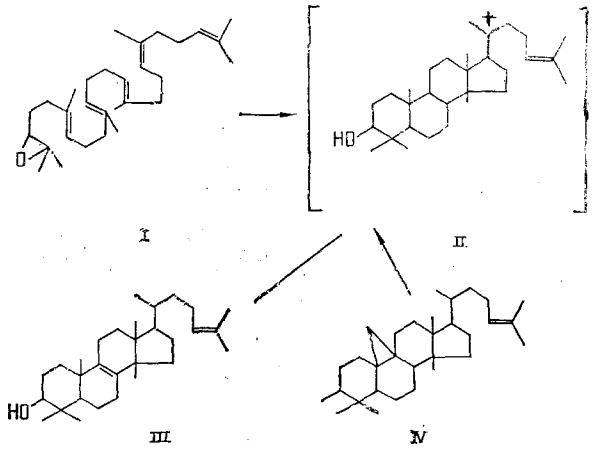
This article reviews the chemistry and biological properties of natural compounds possessing antiatherosclerotic properties.

The search for means of treatment and prophylaxis for atherosclerosis has become an important direction in drug chemistry in the last few decades. A large part of the investigations performed in this area has been devoted to the synthesis of compounds of various types [1-3]. A considerably smaller number has been connected with the study of natural compounds, although certain advances have been achieved in this direction. The search for active substances among natural compounds and the synthesis of new drugs are two equally justified routes for the creation of medicinal agents for the treatment of any disease. However, the basic distinction between the search for active natural compounds with antiatherosclerotic properties and the analogous search for natural compounds with any other type of physiological action, such as cardiovascular agents or substances affecting the nervous system, must be emphasized. According to modern ideas, the factor determining the appearance and development of atherosclerosis is a disturbance of the lipid or, more accurately, the lipoprotein metabolism. Consequently, the healing effect of any particular antiatherosclerotic compound may be directed, in particular, to the regulation of the biosynthesis, the metabolism, and the excretion of lipids and, in the first place, cholesterol. At the same time, both the biosynthetic and metabolic pathways and also the functions of sterols in animal and plant organisms possess much in common. Both phytosterols and zoosterols participate in the construction of cell membranes, serve as precursors of the corresponding steroids, and themselves have a hormonal action on the organism. The initial compounds for the synthesis of all sterols is mevalonic acid. The first steps of its conversion in plant and animal organisms — the formation of squalene from six molecules of mevalonic acid and the oxidation of the squalene to form the 2,3-oxide — are completely identical. The further transformation of squalene 2,3-oxide in animal and plant organisms takes place by different pathways but again have something in common [4, 5]. In the livers of animals and in yeasts and fungi, squalene 2,3-oxide (I) is converted into lanosterol (III) while in plants cycloartenol (IV) is formed.



I II III IV

However, both these transformations take place through an intermediate tetracyclic carbocation (II), which is stabilized in the case of transformation (II)→(III) by two 1,2-migrations of methyl groups, two 1,2-migrations of hydrogen, a splitting out of H^+ from C_9, and the formation of a C_8-C_9 double bond. The mechanism of the conversion (II)→(IV) includes the same four migrations but then the migration of hydrogen from C_9 to C_8 and the splitting

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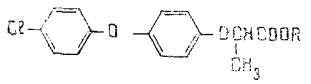
out of the proton H^+ from C_{19} with the formation of a cyclopropane ring takes place. The subsequent transformations of lanosterol into cholesterol and of cycloartenol into phytosterol naturally differ but here again it is possible to find some similarity.

The closeness of the routes of the biosynthesis of sterols in the animal and plant organisms permits us to hope that it will be possible to regulate it by identical or at least structurally similar compounds. For exogenous compounds, this possibility can be confirmed by a number of examples. It is known that individual fungicides derived from imidazole and thiazole possess a hypocholesteremic action in experiments on animals [6, 7]. A whole series of plant growth regulators — the hydrazides of succinic acid (Alar) and of maleic acid, and various ammonium and phosphonium compounds (fosfon, fosfon S) — simultaneously inhibit the synthesis of cholesterol *in vitro* [8, 9]. Some compounds of these two groups that are used in practice are extremely close in structure, and as an example of this we can give the hypocholesteremic agent fenofibric acid (Va) [10] and the plant growth regulator clofop (Vb) [11]. Both these compounds inhibit hydroxymethylglutaryl CoA-reductase — the key enzyme in the biosynthesis of cholesterol.



v a R=H b R = $CH(CH_3)C_2H_5$

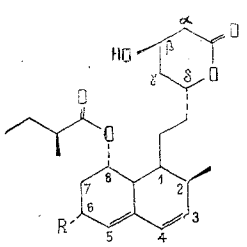
The hypolipidemic properties of exogenous plant growth regulators justify a search for compounds with the same properties among substances endogenous plants that participate in the regulation of the biosynthesis of lipids in plants. The closeness both of the structures of cholesterol and the phytosterols and also of their functions permits us to assume another possibility, as well — that plant sterols themselves may serve as antimetabolites to cholesterol in various stages of its metabolism.

In addition to the biochemical prerequisites of a search for hypolipidemic substances among natural compounds, a medical reason for such a search also exists, which has been briefly formulated in a recent paper [12]: "In consideration of the fact that hypolipidemic compounds may necessitate an almost life-long administration many agents from natural sources have been examined in the hope that they may replace synthetic drugs."

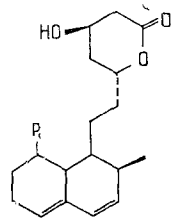
Compounds Inhibiting the Biosynthesis of Cholesterol

The optimum pharmacological action of the biosynthesis of cholesterol must be carried out at the stage of the reduction of 3-hydroxymethylglutaric acid (HMG) to mevalonic acid. On the one hand, this stage determines the rate of the whole process and, on the other hand, the inhibition of HMG CoA-reductase does not cause an accumulation of a substrate which, under the influence of mitochondrial enzymes, can be converted into acetyl-CoA. Until recently, only synthetic inhibitors of HMG CoA-reductase, including various antimetabolites of mevalonic acid — its fluoro, alkyl, or aryl derivatives — were used. In 1976, two independent groups of workers isolated for the first time a natural inhibitor of HMG CoA-reductase. Japanese authors, as the result of a study of the fermentation of more than 8000 antibiotics isolated compound ML-236B from the culture liquid of the antibiotic-producing agent *Penicillum citrinum* [13] and British workers isolated compactin from the culture liquid of *Penicillum brevicompactinum* [14].

It has been shown that these two compounds have the same structure — the δ-lactone of β,δ-dihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1,2,6,7,8,8a-hexahydro-1-naphthylpentanoic acid (VIa).



VI. a R = H
b R = CH_3



VII. a R=H
b R= OAlk, OALkene, OAr

As can be seen from formula (VIa), the tetrahydropyran part of the compactin molecule is the demethyl analogue of mevalolactone. The active form of the compound is represented by the corresponding acid, which is a powerful competitive inhibitor of HMG CoA-reductase [15]. Its inhibiting action has been shown in *in vitro* experiments both on cell-free systems [16] and on a cell culture [17]. In these experiments, compactin in concentrations of 5-20 mg/liter suppressed the conversion of labeled acetate into cholesterol by 50%. The inhibition constant was 1 nM. It was therefore to be expected that in *in vivo* experiments compactin would exert a powerful hypocholesteremic action. This was not observed in experiments on mice, rats, and hamsters [18, 19], but a considerable effect was obtained in experiments on rabbits, dogs, and monkeys [20, 21]. The administration of 50-150 mg of compactin to persons with pronounced hypercholesteremia caused a lowering of the blood plasma cholersterol by 25% [22]. At the same time, the level of triglycerides and phospholipids remained practically unchanged.

The high hypocholesteremic activity of compactin with its low toxicity has stimulated the search for other, analogous, natural compounds. The 6-methyl derivative of compactin (VIb), which has been called monacolin [23] or mevinolin [24] has been isolated from cultures of the antibiotic-producing agents *Monacus ruber* and *Aspergillum terrens*. This compound has proved to be an even stronger inhibitor — the corresponding inhibition constant is 0.4-0.5 nM. Mevinolin exerts a pronounced hypocholesteremic action on experimental atherosclerosis in rabbits [25].

Simultaneously, the synthetic reduction of both component parts of the compactin molecule — the tetrahydropyran [26-28] and the hexahydronaphthalene [29, 30] synthons — has been performed, and also that of the compound itself [31] and various medicinal forms [32]. It has been shown that the activity of compactin is due not only to the δ-lactone ring but also to the hexahydronaphthalene part of the molecule. Compounds containing other aromatic or hydroaromatic rings inhibited HMG CoA-reductase to a considerably smaller degree [33, 34]. It has been postulated that the inhibiting activity is due to the structure of mevinic (β,δ-dihydroxy-1,2,6,7,8,8a-hexahydro-1-naphthylpentanoic) acid (VIIa), and various derivatives of this acid (VIIb) have been synthesized, the majority of which inhibit the biosynthesis of cholesterol [35]. It must be mentioned that the β-methylmevinic acid derivatives containing in their structure the lactone not of demethylmevalinic acid but of mevalonic acid are superior to the mevinic acid derivatives in their inhibiting properties.

The use of compactin has permitted the new important fact of the dual mechanism of the regulation of the activity of the HMG CoA-reductase to be detected [36]. As already mentioned, mevalonic acid is the starting material for the biosynthesis not only of sterols but also of nonsteroid products — in the animal organism, ubiquinone and dolichol. It may be assumed that with the branching of the biosynthetic pathways, the regulation of the activity of the key enzyme — HMG CoA-reductase — may be effected by several regulators, each of which determines the synthesis of one of the final products. The regulator of the biosynthesis of cholesterol is the cholesterol forming a component part of the low-density lipoproteins. Other natural inhibitors of HMG CoA-reductase, such as β-sitosterol [37], also possess a steroid structure. The establishment of the multivalence of regulation and the hypothesis of the existence of a nonsteroid regulator are stimulating the search for similar substances among natural nonsteroid compounds.

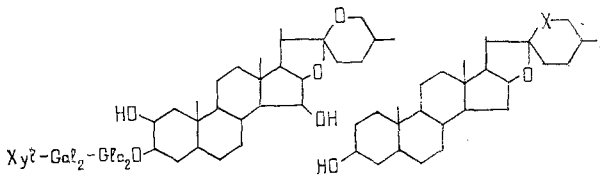
In this connection, a recent publication on the study of the mechanism of the hypocholesteremic action of terpenes is of interest [38]. The very fact of a hypocholesteremic effect both of tricyclic terpenes — derivatives of abietane, pimarane, and totarol [39, 40] — and also of monocyclic terpenes — menthone, pinene, borneol, camphane [41] — was known. Middleton and Hui [38] have shown that the hypocholesteremic action of the monocyclic terpenes is due not to their influence on the absorption cholesterol, as was previously considered, but to the inhibition of HMG CoA-reductase.

Compounds Suppressing the Absorption of Cholesterol in the Intestine

The absorption of both exogenous and endogenous cholesterol in the small intestine is, together with biosynthesis, that stage of its conversions upon which both surgical and medicamentous intervention into the metabolism are carried out. In contrast to an action on biosynthesis, here it is mainly not synthetic compounds but natural compounds of three groups — the saponins, antibiotics, and plant materials — that are used.

Historically, the formation of insoluble complexes of cholesterol with saponins was originally used to suppress the hemolytic activity of the saponins, and then the complex

with digitonin (VIII) found use in the analytical and synthetic chemistry of the sterols [42]. Only after more than half a century were attempts made to use the formation of insoluble complexes with cholesterol by saponins for decreasing the adsorption of cholesterol. The complex with digitonin has the lowest solubility, and it may be assumed that it possesses the maximum hypocholesteremic action. However, in the first place, it is somewhat more toxic than the complexes with other saponins and, in the second place, the natural sources of digitonin are limited. At the present time, no relationship has been found between the structure of the saponins and the solubilities of their complexes with cholesterol — there are only isolated observations that the spirostanol saponins precipitate cholesterol in lower concentrations than the furostanol saponins and that an increase in the number of glycosidic residues promotes precipitation [43]. It has been found that tomatine, the aglycone of which — tomatidine (IXa) — forms a sparingly soluble complex with cholesterol, possesses a hypocholesteremic action in experiments on monkeys [44]. A similar action has been observed for an oxygen analogue of tomatine — diosgenin (IXb). Diosgenin-containing saponins, such as funkioside, form complexes with cholesterol that are only twice as soluble as the complex with digitonin [43]. Diosgenin itself and some diosgenin-containing saponins have found use in clinical practice as hypocholesteremic agents. Thus, the domestic preparations Polisponin [45] and Diosponin [46] contain the sum of such saponins from the yam, and Tribusponin — from the more common puncture vine — has recently been proposed [47].



VIII IX a. X = NH
b. X = O, Δ^5

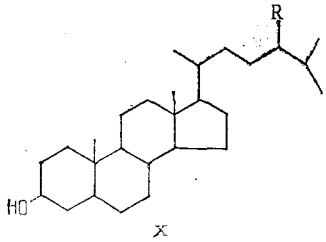
In recent years, the capacity of the saponins for forming complexes with cholesterol has found use in one of the approaches to the treatment of atherosclerosis. One of the methods for lowering the blood plasma cholesterol that has been developed at the present time is its extraction by sorption. In order to increase selectivity with respect to cholesterol, sorbents have been produced which contain saponins immobilized on a polymeric base (amino-Silochrome) [48-50]. The saponins are covalently bound to the amino-Silochrome by the periodate oxidation of the glycosidic moiety and the interaction of the aldehyde so formed with the amino groups of the support. In accordance with what has been said above, the maximum sorption capacity for cholesterol is possessed by sorbents containing digitonin and gitonin — saponins of the spirostanol series with a large number of hexose residues. Thus, amino-Silochrome modified with digitonin binds about 10 mg of blood plasma cholesterol per 1 g of sorbent.

Another group of natural compounds forming complexes with cholesterol and thereby preventing its absorption are the polyenic antibiotics. As is well known the formation of complexes by the latter with sterols forms the basis of their antibiotic action [52, 53]. The administration of polyenic antibiotics, such as candicidin [54], to animals causes a fall in their cholesterol levels.

The same effect is possessed by other, nonpolyenic, antibiotics containing basic groups, such as neomycin [55]. The mechanism of the hypolipidemic action of the latter is apparently due to the binding of bile acids. However, in contrast to the saponins, the antibiotics have not come into wide practical use as hypolipidemic agents.

The absorption of cholesterol in the intestine is that stage of its metabolism upon which plant sterols act as antimetabolites preventing absorption. Here is necessary that the antimetabolite itself possesses a low absorbability. Sitosterols can lower the solubility of cholesterol, displacing it from the micelles and can conjugate with cholesterol both in the process of its absorption by the cells of the mucosa and in the process of its esterification before the inclusion in the chylomicrons [56]. Some results — for example, relating to the dependence of the inhibiting capacity of a phytosterol on its physical state (powder, suspension) — indicate the first mechanism, while others — in particular the change in the rate of esterification of sterols in the same sequence as their absorption — are in favor of the latter [57]. However, even without establishing the mechanism of the inhibition

of the absorption of cholesterol it is possible to draw certain conclusion concerning the dependence of the inhibiting capacity on the structure of a sitosterol. Campesterol (Xb), differing from cholesterol (Xa) by one methyl group, although it is inferior to cholesterol in the rate of absorption nevertheless inhibits this absorption only slightly. Sitosterol (Xc) differs from cholesterol by an ethyl group, and the rate of its absorption is only 10% of the rate of the absorption of cholesterol and it strongly inhibits the absorption of cholesterol in the intestine [56]. An even greater change in the structure — hydrogenation of the 5-6 double bond [sitostanol (Xd)] or the introduction of a double bond in position 22 [brassicasterol (Xe) or stigmasterol (Xf)] cause a more considerable increase in inhibiting properties in relation to the absorption of cholesterol [58, 59]. But this increase is not unlimited — the passage to compounds differing considerably in structure — ergosterol (Xg) or 7-oxocholesterol leads to a fall of inhibiting capacity [59].



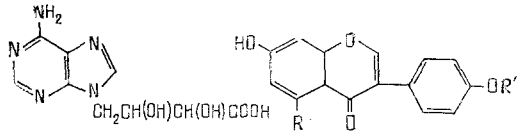
X

a. R = H, Δ^5
b. R = CH_3, Δ^5
c. R = C_2H_5, Δ^5
d. R = C_2H_5
e. R = CH_3, $\Delta^{5,22}$
f. R = C_2H_5, $\Delta^{5,22}$
g. R = CH_3, $\Delta^{5,7,22}$

Of the phytosterols mentioned, β-sitosterol has found practical use as a hypocholesteremic agent [60]; it possesses a higher biological action and there are adequate sources of the plant raw material.

It must be mentioned that since β-sitosterol exhibits its hypocholesteremic properties at the stage of the absorption of cholesterol, the actual plant sterol must be used and not its O-derivative. It has been shown that esters of β-sitosterol affect absorption only to the extent that they have undergone hydrolysis [59]. Nevertheless, various O-derivatives of β-sitosterol the hypolipidemic action of which exceeds that of the sterol itself have been described in the literature [61, 62]. It is possible that this enhancement of the effect is not connected with a suppression of the absorption of cholesterol but is due to other mechanisms and, in particular, to an influence on the biosynthesis of the cholesterol [37].

Together with the two groups of natural compounds inhibiting the biosynthesis of cholesterol and its absorption in the intestine that has been considered above, other natural antiatherosclerotic compounds have been described in the literature. Thus, a considerable hypocholesteremic action of 4-(adenin-9-yl)-2,3-dihydroxybutyric acid (lentysine), (XI) isolated from fungi, has been shown [63-65]. Many workers have demonstrated the hypocholesteremic action of various plant isoflavones — biochanin (XIIa), formononetin (XIIb), daidein (XIIc), and others [66-68]. The action of all these compounds is connected by the authors with the presence of a free (or methozylated) phenolic hydroxyl. This is confirmed by the intensification of the action of isoflavones having several phenolic hydroxyls [69], and also by the hypocholesteremic properties of such plant phenols as gossypol [70] and vitamin E [71]. It has recently been shown that in the phytoecdysone — polyhydroxycholest-5-en-6-one — series the hypocholesteremic activity rises with an increase in the number of hydroxy groups [72]. Characteristic for the majority of the compounds mentioned is a decrease in the total cholesterol level retention of the cholesterol level of the HDLPs [high-density lipoproteins], which is a valuable property. However, the mechanism of their action remains obscure.



XI

XII a R = OH, R' = CH_3
b R = H, R' = CH_3
c R = R' = H

In recent years, greater attention has been devoted to the study of the influence on the lipid metabolism of food factors, particularly dietary fiber. A considerable action on the cholesterol level of such substances as lignin, and the dietary fiber of alfalfa, bran, etc., has been shown. The majority of authors connect this influence with the capacity of the cell tissue for sorbing both lipids and, in particular, bile acids and promoting their

elimination from the organism. Since, however, dietary fiber is not a medicinal but a food substance, we shall not consider this question, which has been discussed in detail in recent reviews [73, 74].

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STRUCTURE OF THE XYLOGLUCAN OF THE LEAVES OF *Heracleum sosnowskyi*

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The results are given of investigations of the polysaccharide complex of the leaves of *Heracleum sosnowskyi*. The complex was isolated from the leaves by extraction with alkali.

We have previously studied the structure of the xylans and glucans of a number of fodder plants [1, 2]. The cell walls of developing plant tissues contain a xyloglucan [3]; this has been found in the midribs of tobacco leaves [3] and in seeds [4]. In view of the probability of the presence of this saccharide in the leaves of herbs, we have isolated it from the leaves of *Heracleum sosnowskyi* Manden. collected in the Main Botanical Garden of the Academy of Sciences of the Moldavian SSR in Kishinev in 1981.

The monomeric composition of the hemicelluloses (HMCs) isolated was represented by uronic acid, galactose, arabinose, and xylose in a percentage ratio of 14.5:7.3:30.9:12.8:35.5. The scheme of fractionation of the HMCs included the following steps: the production of a water-soluble fraction of the HMCs, the chromotography of this fraction on DEAE-cellulose to separate the acidic fragments from the neutral fragments, and then subfractionation on a cellulose column. As a result of the fractionation, a neutral xyloglucan was isolated. After

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