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REVIEW

Development of dietary supplements to eliminate the atherogenicity of low-density lipoprotein

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Abstract

This review systematizes current data on the role of desialylation of lowdensity lipoproteins (LDL) as a key initiating mechanism of atherogenesis that precedes oxidative modification. The structural and functional significance of sialic acid in apolipoproteinB100 is considered, and the enzymes of the sialidase (neuraminidase) family responsible for its cleavage are characterized. The pathogenic role of increased sialidase activity in atherosclerosis, type 2 diabetes mellitus, and other diseases is discussed. Since desialylation occurs at an early stage of LDL modification, preserving the native sialylation pattern may prevent subsequent lipoprotein retention, macrophage uptake, and foam cell formation. This approach has the potential to complement conventional lipid lowering therapy by targeting residual cardiovascular risk through mechanisms independent of plasma LDL cholesterol reduction. The advantages of using dietary supplements based on natural sialidase inhibitors for long-term prevention compared with synthetic drugs are shown. Examples of already existing dietary supplements with antiatherosclerotic effects are described. A separate section is devoted to computer-based approaches, including molecular docking, for the identification of potential sialidase inhibitors among flavonoids. Previously published virtual screening data are discussed, with particular attention to gallated catechins as potential candidates for further experimental investigation. The feasibility of further experimental and clinical studies to create effective and safe nutraceuticals that affect the early stages of atherogenesis is substantiated.

Keywords: Atherosclerosis, lowdensity lipoproteins, sialic acid, desialylation, sialidase, flavonoids, dietary supplements, molecular docking

Introduction

Cardiovascular diseases caused by atherosclerotic arterial lesions remain the leading cause of death worldwide, despite significant advances in their treatment. Coronary heart disease, myocardial infarction, and cerebral strokes claim millions of lives each year, and these conditions are steadily becoming younger [1]. Current therapy, including statins, antiplatelet agents, antihypertensive drugs, and endovascular interventions, can reduce the risk of complications; however, many patients, even after achieving target lipid profile values, continue to progress. This fact indicates the existence of incompletely understood pathogenetic links and dictates the need to search for new molecular targets [2].

The accumulation of cholesterol and its esters in the arterial intima occupies a central place in the pathogenesis of atherosclerosis. The main carrier of cholesterol in the blood is lowdensity lipoproteins (LDL). However, native LDL do not possess atherogenic properties—they acquire them only after certain modifications [3]. For a long time, the hypothesis that LDL oxidation is the trigger of atherogenesis dominated. Oxidized particles are actively taken up by macrophages via scavenger receptors, turning into foam cells, which initiate an inflammatory cascade [3]. Nevertheless, this model has serious limitations: the concentration of oxidized LDL in the blood of patients is low; powerful antioxidants (vitamins E and C, betacarotene) have not shown clinical efficacy in large randomized trials; and in many experimental models, atherosclerosis

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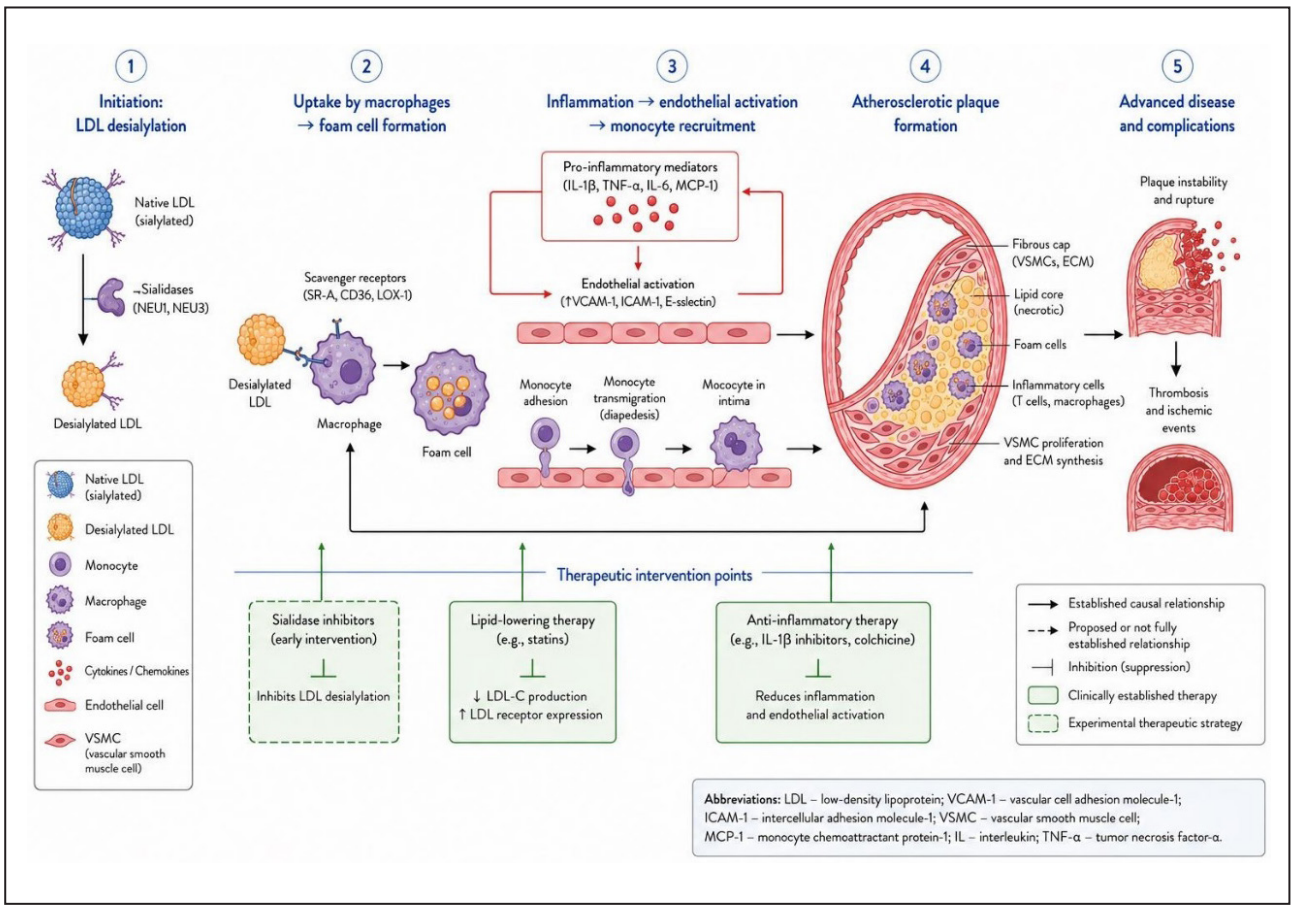

Figure 1. General pathogenetic scheme of atherosclerosis with emphasis on desialylation.

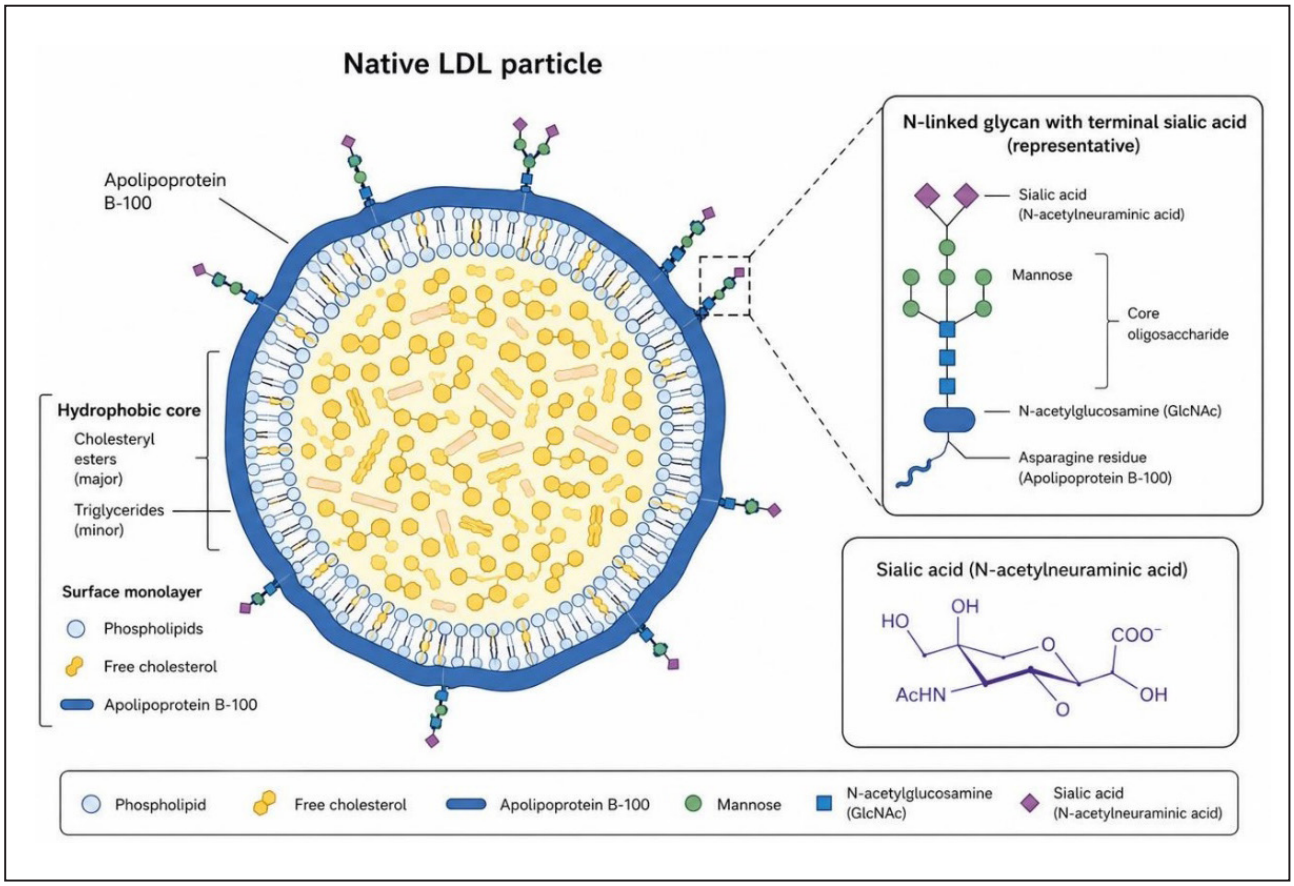

Figure 2. Schematic structure of native LDL with highlighted sialic acids.

develops without significant oxidation.

A systematic revision of this concept was undertaken by A.N. Orekhov, who, based on many years of research, concluded that oxidation is a secondary process, and the primary event is LDL desialylation (Figure 1) [4-6]. The essence of this phenomenon is the loss of terminal sialic acid residues, which normally protect the lipoprotein particle from nonspecific interactions. The loss of even 10–15% of sialic acid significantly increases the atherogenicity of LDL [4]. Thus, influencing the early stages of modification, namely preserving sialic acid, may become a more effective prevention strategy than fighting already formed plaques or inflammation.

In this review, we sequentially consider the structural and functional role of sialic acid in LDL, characterize the sialidase enzymes responsible for its cleavage, and substantiate the prospects of using dietary supplements based on natural sialidase inhibitors for long-term prevention of atherosclerosis. Special attention is paid to computer methods that allow accelerating the search for new inhibitors among flavonoids, as well as to the analysis of clinical data confirming the effectiveness of this approach.

Molecular mechanisms of atherogenic modification of LDL

Structural and functional role of sialic acid in lowdensity lipoproteins

Sialic acid (N-acetylneuraminic acid) is a ninecarbon monosaccharide containing a carboxyl group, which at physiological pH gives the molecule a negative charge. In LDL, sialic acid is attached to apolipoproteinB100 (apoB100) via O or Nglycosidic bonds (Figure 2). ApoB100 contains about 16 Nglycosylation sites, and more than 80% of them are terminally sialylated [7]. These carbohydrate chains protrude beyond the surface of the lipoprotein particle, forming a socalled glycan “brush” that creates an electrostatic and steric barrier. Due to this, native LDL do not interact with negatively charged proteoglycans of the subendothelial matrix and do not aggregate with each other.

When sialic acid is cleaved off by sialidase, the particle charge decreases, leading to conformational changes in apoB100 (Figure 3). Previously hidden hydrophobic regions and positively charged amino acid residues become exposed, which can bind to proteoglycans (heparan sulfate and chondroitin sulfate) of the intima (Table 1). As a result, desialylated LDL are retained in the vascular wall, aggregate, and become more vulnerable to oxidation. However, as Orekhov and co-authors emphasize, the most critical consequence of desialylation is a sharp increase in the uptake of such particles by macrophages [4, 8]. Experimental studies have demonstrated that human NEU1 and NEU3 can desialylate apoB100 in LDL, and that desialylation markedly increases LDL uptake by human macrophages. Genetic inactivation or pharmacological inhibition of NEU1 and NEU3 also delays the formation of aortic fatty streaks in *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice without reducing plasma LDL levels [6]. This process is mediated by several types of scavenger receptors (SR-A, CD36, LOX-1), which recognize modified lipoproteins with high predicted affinity. As a result, macrophages become overloaded with cholesterol esters and transform into foam cells—the morphological substrate of the atherosclerotic plaque [9, 10].

It is important to note that desialylation is not a random event. In patients with atherosclerosis, trans-sialidase activity is detected in blood plasma, and its level correlates with the severity of coronary atherosclerosis [11]. In the classic work of Tertov *et al.*, it was shown that this enzyme not only cleaves sialic acid but can also transfer it to other glycoproteins and glycolipids, indicating its regula-

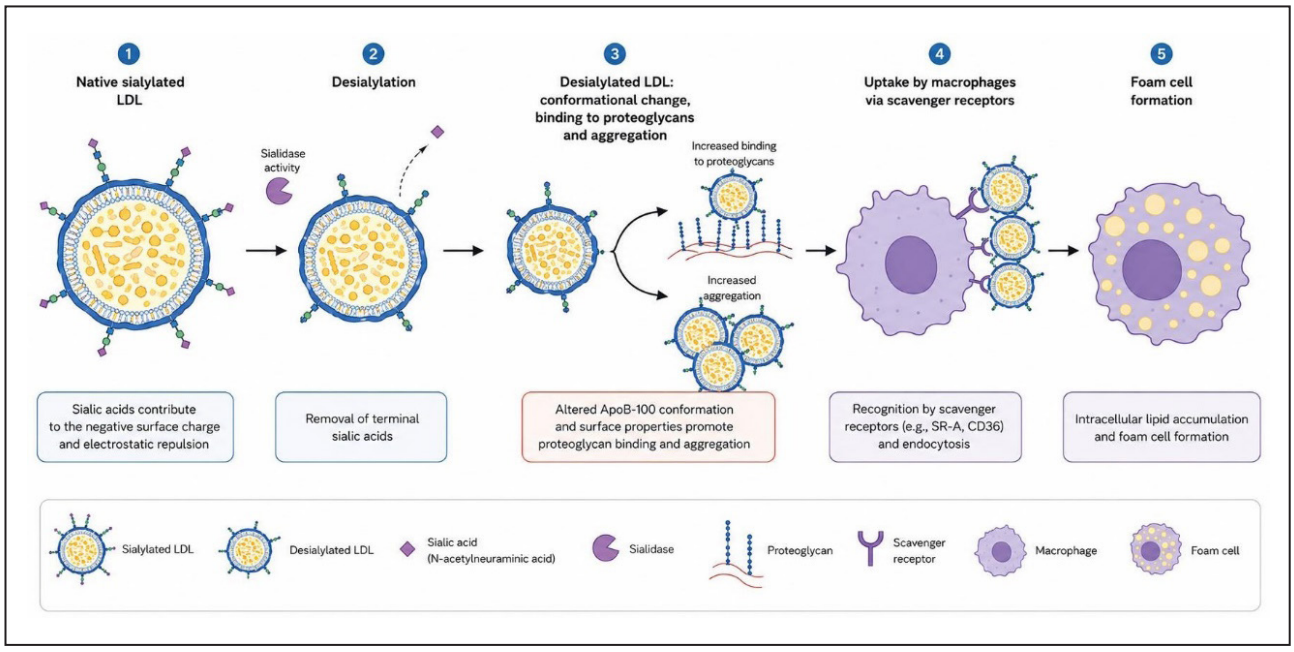

Figure 3. Stepbystep scheme of desialylation, aggregation, and macrophage uptake, to clearly show the entire cascade.

Table 1. Comparison of properties of native and desialylated LDL.

Parameter	Native LDL	Desialylated LDL	Measurement/Notes
Sialic acid content	14–45 μg/mg LDL protein (healthy range reported in different studies)	40–75% lower than native LDL; approximately 2–6-fold lower sialic acid content	Measured by thiobarbituric acid assay or lectin affinity chromatography
Particle charge	Normal electronegativity	Significantly more electronegative than native LDL	Usually determined by ion-exchange chromatography or electrophoretic mobility; no universally accepted numerical value reported
Tendency to aggregate	Low	Increased aggregation tendency	Reported qualitatively; no standardized quantitative metric available across studies
Macrophage uptake	Baseline (1-fold)	Approximately 2–3-fold higher cellular uptake and lipid accumulation, depending on the experimental model	Measured by radiolabeled LDL uptake or intracellular cholesterol accumulation; values vary among cell models
Atherogenicity	Non-atherogenic under physiological conditions	Strongly atherogenic; induces foam cell formation and intracellular cholesterol accumulation	No universal numerical index exists; evaluated by cholesterol accumulation assays in cultured arterial cells

Notes: LDL, low-density lipoprotein; apoB, apolipoprotein B.

Table 2. Main characteristics of human sialidase isoforms (NEU1–NEU4): localization, tissue expression, role in atherogenesis.

Isoform	Subcellular localization	Major tissue expression	Preferred substrates/biological function
NEU1	Lysosomes (lysosomal membrane complex with PPCA and β-galactosidase); can translocate to the plasma membrane after cell activation	Ubiquitously expressed; highly expressed in macrophages, leukocytes, liver, spleen	Glycoproteins and oligosaccharides; regulates lysosomal catabolism, receptor activation, and immune responses
NEU2	Cytosol	Predominantly skeletal muscle; low expression in other tissues	Cytosolic glycoproteins and oligosaccharides; involved in muscle differentiation and regeneration
NEU3	Plasma membrane (lipid rafts); endosomal membranes	Brain, heart, skeletal muscle, vascular endothelium	Gangliosides (GM3, GD1a); modulates cell signaling, apoptosis, insulin signaling, and cell proliferation
NEU4	Mitochondria, lysosomes, endoplasmic reticulum	Brain, liver, kidney, skeletal muscle	Gangliosides and glycoproteins; involved in mitochondrial function, apoptosis, and neurite formation

Notes: PPCA, protective protein/cathepsin A; GM3, monosialodihexosylganglioside; GD1a, disialosylganglioside.

tory role in maintaining overall sialylation homeostasis [11]. Moreover, the authors experimentally confirmed that LDL treated with patient plasma acquire the ability to stimulate the accumulation of cholesterol esters in cultured vascular wall cells, and this effect directly depended on the degree of desialylation. These data convincingly prove that transsialidase activity is not an epiphenomenon but a pathogenetically significant factor.

Thus, desialylation is an early initiating event that precedes oxidation and aggregation, and also triggers inflammatory reactions through macrophage activation [12]. Therefore, targeting this stage may be more effective than therapy directed at later links.

Sialidases: families, tissue distribution, pathological role

In humans, four isoforms of sialidase (neuraminidase) encoded by the genes *NEU1*, *NEU2*, *NEU3*, and *NEU4* have been identified (Table 2). They differ in subcellular localization, tissue expression, and substrate specificity [13]. NEU1 is predominantly localized in lysosomes and participates in glycoprotein catabolism; its deficiency leads to sialidosis, a severe hereditary disease. NEU2 is a cytosolic form found in skeletal muscles and leukocytes. NEU3 is membraneassociated and expressed in the brain, heart, and vascular endothelium. NEU4 is localized in mitochondria and the liver [13]. From the standpoint of atherogenesis, NEU1 and NEU3 are of particular interest because experimental studies have demonstrated their ability to desialylate apoB-100 in LDL and increase LDL uptake by macrophages [6]. Interestingly, human transsialidase, described by Nikonova *et al.*, exhibits dual activity: it not only hydrolyzes glycosidic bonds but also catalyzes the transfer of sialic acid to acceptor molecules, expanding its physiological role [14]. This feature is important for understanding the possible side effects of inhibitors, since blocking the enzyme may disrupt not only LDL desialylation but also other processes dependent on transsialidase activity.

Importantly, natural and synthetic sialidase inhibitors do not necessarily exhibit uniform activity across sialidase isoforms. Classical transition-state analogues such as Neu5Ac2en (DANA), as well as the naturally occurring inhibitor siastatin B, show relatively broad inhibitory

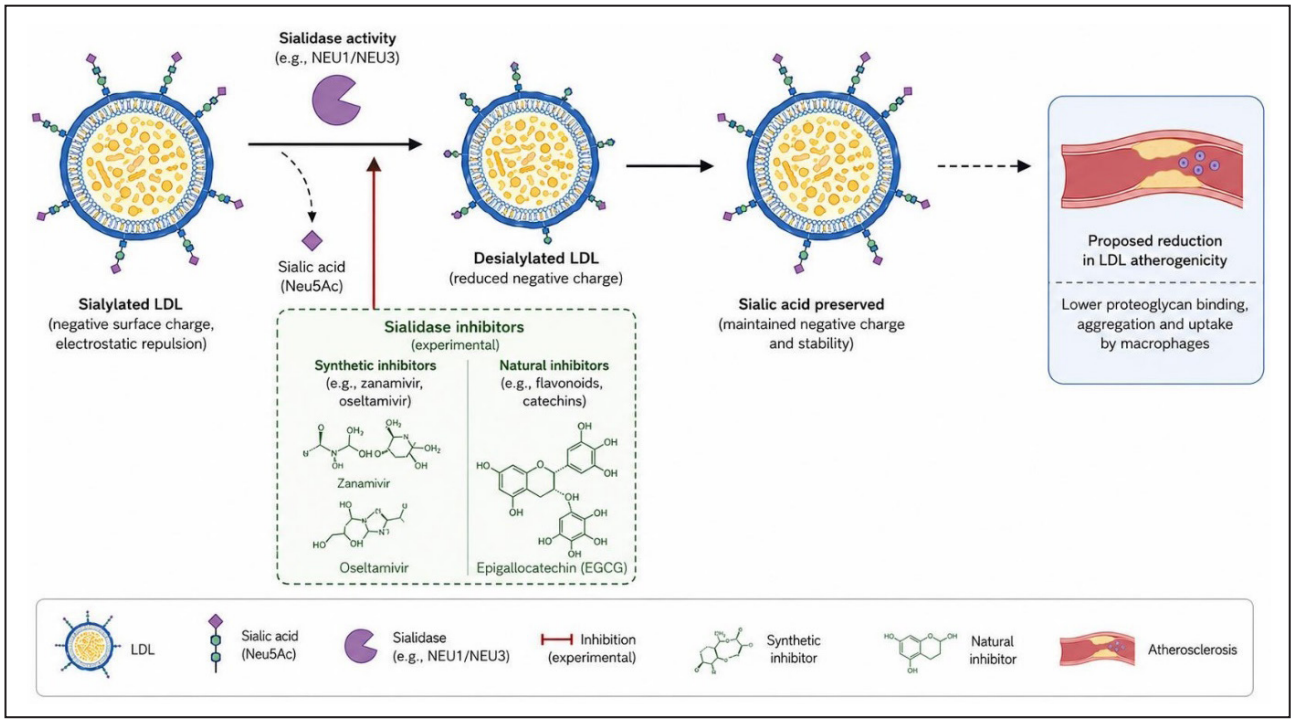

Figure 4. Scheme of action of sialidase and its inhibitors (synthetic and natural), showing how inhibitors prevent desialylation.

activity and can therefore be considered pan-sialidase inhibitors. In contrast, structural modification of sialic acid analogues can produce pronounced isoform selectivity. For example, Neu5AcN32en (compound 13), obtained by modification of DANA, was reported to be highly selective for human NEU2, whereas modifications at the C4, C5, C7 and C9 positions of DANA can differentially affect inhibition of human NEU1–NEU4. C9-substituted derivatives bearing bulky groups have shown particularly high selectivity toward NEU3, while amide-containing derivatives and triazole-containing analogues have been reported as selective inhibitors of NEU1 and NEU4, respectively. These findings indicate that sialidase inhibition should not be regarded as a uniform pharmacological mechanism: the selectivity of an inhibitor depends strongly on the structural characteristics of the active site and on the nature and position of substituents in the inhibitor molecule. Consequently, for the development of anti-atherosclerotic nutraceuticals, compounds intended to inhibit NEU1 and/or NEU3 should be experimentally evaluated for isoform selectivity rather than assumed to act specifically on the sialidases involved in LDL desialylation [15-17].

At the molecular level, the catalytic mechanism of mammalian sialidases has been characterized structurally and enzymatically. Recent structural analysis of NEU1 demonstrated that the enzyme adopts a six-bladed β-propeller fold with the active site located in a central cavity. The catalytic mechanism involves a conserved arginine triad that stabilizes the carboxylate group of sialic acid, together with a nucleophilic tyrosine, a glutamate residue, and an aspartate residue that participate in cleavage of the glycosidic bond. In particular, structural and mutational analyses of human *NEU1* showed that substitution of the catalytic Asp103 markedly reduced enzymatic hydrolysis, whereas mutations affecting residues interacting with the glycerol moiety of the substrate also substantially decreased activity. These findings demonstrate that sialic acid cleavage depends on a defined catalytic architecture and specific amino-acid residues rather than representing a nonspecific modification of LDL glycans [18, 19].

Increased sialidase activity has been found not only in atherosclerosis but also in many other diseases. For example, in type 2 diabetes mellitus, plasma neuraminidase activity correlates with HbA1c levels, indicating a link between hyperglycemia and activation of this enzyme [20]. Thus, sialidase inhibitors may have a wide range of therapeutic applications, but high selectivity is required to avoid undesirable effects.

Sialidase as a pharmacological target: advantages over traditional approaches

The traditional strategy for combating atherosclerosis is based on three main directions: lowering LDL cholesterol (statins, ezetimibe, PCSK9 inhibitors), suppressing thrombus formation (aspirin, clopidogrel), and controlling blood pressure. However, these approaches have significant limitations. Statins, being the gold standard, effectively reduce cardiovascular risk, but only in 60–70% of patients, and some of them develop myopathy, hepatotoxicity, or new cases of diabetes mellitus. Monoclonal antibodies to interleukins (*e.g.*, canakinumab) have shown efficacy in reducing inflammation, but their high cost and the need for parenteral administration limit widespread use.

Against this background, targeting sialidase looks particularly attractive because it is at the very beginning of the pathogenetic cascade. Inhibition of this enzyme allows sialic acid to be preserved on LDL, preventing their atherogenic modification (Figure 4). At the same time, the effect

is twofold: first, LDL uptake by macrophages and foam cell formation are reduced; second, associated inflammation is reduced, since desialylated particles actively stimulate the production of proinflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (MCP-1), and enhance the expression of adhesion molecules on the endothelium [12, 21]. Thus, sialidase blockade can simultaneously affect both the lipid and inflammatory components of atherogenesis. Experiments on *Apoe*$^{-/-}$ mice have shown that pharmacological inhibition of *NEU1* and *NEU3* significantly reduces the area of fatty streaks in the aortic root and reduces the macrophage content in plaques. Moreover, unlike statins, targeting sialidase does not require a significant reduction in LDL cholesterol, which may be particularly useful for patients with normal lipid profiles but high residual risk. This opens up opportunities for personalized prevention.

Dietary supplements as a tool for long-term prevention of atherosclerosis

Atherosclerosis develops over decades, so an optimal preventive strategy should be not only effective but also safe with long-term use, economically affordable, and convenient for the patient. Synthetic drugs often do not meet these criteria due to side effects, the need for medical supervision, and high cost. In this context, dietary supplements (nutraceuticals) represent an attractive alternative. Dietary supplements are compositions of natural or natureidentical substances that are taken orally to enrich the diet and can exert physiological effects [20, 22-24]. Their undeniable advantages include low toxicity when recommended doses are observed, availability (overthecounter), relatively low price, and the possibility of long-term use without habituation [25, 26].

However, the potential advantages of nutraceuticals should be considered together with several important pharmacological and translational limitations. The bioavailability of many plant-derived bioactive compounds is limited by poor aqueous solubility, incomplete gastrointestinal bioaccessibility, low intestinal permeability, and extensive first-pass metabolism; consequently, pronounced activity observed *in vitro* may not translate into therapeutically relevant systemic concentrations *in vivo*. Their efficacy may also vary according to the food matrix, formulation, dietary context, and processing conditions. Another important limitation is the lack of uniform standardization of some nutraceutical products, which can result in substantial batch-to-batch variation in the concentration of active constituents and, in some cases, adulteration or contamination. Finally, natural origin does not guarantee pharmacological selectivity or complete safety. Bioactive compounds may exert off-target effects, interact with drug-metabolizing enzymes and transporters, or interfere with the action of concomitant medications. Therefore, the development of sialidase-targeting nutraceuticals requires not only demonstration of inhibitory activity, but also characterization of bioavailability, chemical standardization, pharmacokinetics, potential off-target effects, and drug interactions [27-32].

Nevertheless, there are examples of dietary supplements with a solid evidence base. One of the most studied is garlic powder (Allikor). In the doubleblind placebocontrolled AMAR study, it was shown that taking Allikor for several years significantly slowed the progression of carotid intimamedia thickness (decrease of 0.022 mm/year vs increase of 0.015 mm/year in the placebo group, P = 0.002) [33, 34]. In a population study conducted in 2002 in Putivl, the use of Allikor during the flu season reduced the incidence of acute respiratory viral infections by 7 fold and mortality from cardiovascular causes by 2.2 fold [35]. Another example is “Inflaminat” based on extracts of calendula, elderberry, and violet, which has antiinflammatory properties and improves blood rheology [30]. “Karinat”, a complex of phytoestrogens from red clover) showed antioxidant effects and improved endothelial function [26]. Lipid lowering reduces the concentration of LDL particles; antioxidant approaches aim to limit oxidative modification; anti-inflammatory approaches attenuate downstream inflammatory signaling. In contrast, preservation of LDL sialylation is proposed to act upstream by limiting the conversion of native LDL into a particle with enhanced macrophage uptake. This creates a niche for the development of a new class of nutraceuticals aimed specifically at inhibiting sialidase [36].

Very recently, studies have appeared confirming the effectiveness of nutraceuticals in modulating sialylation. Zhang *et al*. demonstrated that oral administration of N-acetylneuraminic acid attenuates atherosclerosis in *LDLR*$^{-/-}$ mice by altering the composition of the gut microbiota and bile acid metabolism [37]. Ormiston *et al*. showed that a combination of a statin with epicatechin safely reduces the 10 year risk of cardiovascular events [38]. In a pilot clinical study, Valerio *et al*. found that a combination of several bioactive polyphenols improved endothelial function, supporting the concept of a synergistic effect of multicomponent dietary supplements [39]. These data are encouraging and indicate the correctness of the chosen direction.

Virtual screening and molecular docking as approaches for identifying potential sialidase inhibitors

NEU1 and NEU3 represent the most relevant sialidase isoforms for the atherogenic pathway considered in this review. Experimental studies have shown that genetic inactivation or pharmacological inhibition of *NEU1* and *NEU3* reduces LDL desialylation, macrophage uptake of LDL, and atherosclerotic fatty streak formation without a corresponding reduction in plasma LDL cholesterol levels. Therefore, these isoforms provide a mechanistically defined target for the search for compounds capable of preserving LDL sialylation [6].

The traditional approach to finding new active compounds—random discovery or screening of large libraries *in vitro*—requires huge expenditures of time and re-

sources. In recent years, computer methods have come to the fore, allowing virtual screening and prediction of the interaction of potential ligands with protein targets. The most common tool is molecular docking, which calculates the spatial orientation and binding energy of the ligand in the active site of the enzyme. The AutoDock Vina program [40], developed by Trott and Olson, is widely used due to its good balance between speed and accuracy [41]. Binding energy is expressed in kcal/mol, with more negative values corresponding to a stronger complex. However, one should remember the limitations of the method: it does not take into account protein flexibility (unless special protocols are used), solvent effects, entropic effects, and can give false positive results. Therefore, experimental verification *in vitro* and *in vivo* remains mandatory [42, 43].

A recent three-stage virtual screening study by Mikhailova *et al*. identified natural compounds as candidate human sialidase ligands. In the first stage, PubChem data were used to identify 36 natural compounds with reported inhibitory activity, including 20 flavonoids. In the second stage, these flavonoids were ranked by molecular docking according to their predicted binding scores, with epicatechin-3-gallate showing the most favorable score (–6.923 kcal/mol). However, the computational analysis was performed against human sialidase NEU2 rather than the NEU1 or NEU3 isoforms implicated in LDL desialylation. Therefore, these results provide preliminary evidence for the suitability of flavonoid scaffolds for further investigation, but cannot be interpreted as direct evidence of NEU1 or NEU3 inhibition [41].

The use of NEU2 in the available docking study represents an important limitation because the atherogenic effects of LDL desialylation have been specifically linked to NEU1 and NEU3. Accordingly, the reported docking results should be regarded as a preliminary structure-based prioritization of flavonoid candidates rather than as validation of NEU1/NEU3 inhibition. Direct docking against NEU1 and NEU3 and subsequent biochemical testing would be required to establish isoform-specific activity.

A previously published *in silico* study performed virtual screening of 46 natural flavonoids from the PubChem database for their potential interaction with sialidase. To validate the docking protocol, re-docking of the co-crystallized ligand was performed, and the program reproduced its experimental conformation with a root-mean-square deviation (RMSD) of 1.8 Å, which is significantly below the generally accepted threshold of 2.0 Å [37]. This confirmed the adequacy of the settings (Table 3). As a result of the screening, 20 flavonoids with binding energies below –8.0 kcal/mol were identified. The leaders were gallated catechins: epicatechin-3-gallate, epicatechin gallate, trifolirhizin, epigallocatechin, and epigallocatechin gallate. These compounds are known for their antioxidant and antiinflammatory properties, but their ability to inhibit sialidase is described for the first time. For further experimental verification, epigallocatechin (CID 72277) was selected as the most commercially available and with high predicted activity. Table 3 shows the binding energies for the ten flavonoids with the best results.

It is worth noting that molecular docking is successfully applied to other enzyme targets in cardiovascular and metabolic diseases. For example, citrus flavonoids (hesperidin, naringenin) showed binding energies with angiotensinconverting enzyme up to –8.5 kcal/mol, and these calculations were confirmed by hypotensive effects in animal models. Green tea polyphenols (epigallocatechin) and cinnamon inhibit α-glucosidase (energy –7.2 kcal/mol), which explains their ability to reduce postprandial glycemia. Glycyrrhizic acid from licorice exhibits antidiabetic activity by acting as a PPAR-γ agonist [44]. These examples emphasize that the combination of computer prediction and experimental verification is an effective strategy for discovering new nutraceuticals.

The docking results do not provide experimental evidence of enzymatic inhibition. The identified flavonoids should therefore be considered candidate compounds requiring biochemical validation. Validated spectrophotometric approaches for measuring sialidase activity and inhibition are available [45]. The next experimental step should include testing of the prioritized compounds against recombinant human NEU1 and NEU3, determination of concentration-dependent inhibition and IC_{50} values, and assessment of isoform selectivity. Compounds demonstrating inhibitory activity should subsequently be evaluated for their ability to prevent LDL desialylation and reduce macrophage uptake of LDL.

Prospects for the use of dietary supplements for correcting sialidase activity in atherosclerosis

Currently, the main approach to influencing the LDL sialylation system is direct inhibition of sialidase using synthetic or natural inhibitors. Synthetic drugs such as zanamivir and oseltamivir are potent inhibitors of viral neuraminidase and are widely used for influenza. How-

Table 3. Top10 flavonoids: name, predicted docking score, kcal/mol, predicted interaction type.

PubChem CID	Name	predicted docking score, kcal/mol
65056	Epicatechin-3-gallate	–6.923
107905	Epicatechin gallate	–6.571
442827	Trifolirhizin	–6.270
72277	Epigallocatechin	–6.082
65064	Epigallocatechin gallate	–6.058
5281605	Baicalein	–5.983
5317750	Glycitein	–5.959
5281803	4'-Methoxy-3',5,7-trihydroxyisoflavone	–5.867
44257483	Glyceollidin I	–5.859
5281222	Butein	–5.800

Notes: Data compiled from [42].

ever, their long-term use in atherosclerosis is unacceptable due to potential side effects (bronchospasm, neuropsychiatric disorders) and high cost [45]. Natural compounds may offer attractive candidates for long-term nutraceutical development, although their selectivity, bioavailability, pharmacokinetics and safety require experimental validation. [25, 37]. Previously published molecular docking studies suggest that gallated catechins may have favorable predicted interactions with sialidase. These findings provide a rationale for further investigation of gallated catechins as potential natural sialidase inhibitors; however, their inhibitory activity, selectivity, bioavailability, and safety require experimental validation before their use in nutraceutical formulations can be considered.

An alternative approach is the use of exogenous sialic acid (N-acetylneuraminic acid) as a nutraceutical. As shown in the work of Zhang *et al*., such administration can be effective, but most likely acts through systemic mechanisms (microbiota, gut–liver axis) rather than through direct incorporation of sialic acid into LDL [37]. Moreover, exogenous acid is rapidly metabolized, and high doses are required to achieve clinically significant concentrations. Therefore, sialidase inhibition appears to be a more physiological and targeted approach, since it prevents the loss of endogenous sialic acid without disturbing its overall metabolism.

In the future, it is possible to develop combined dietary supplements containing several sialidase inhibitors with different mechanisms of action, or their combination with other cardioprotective nutraceuticals (*e.g*., polyphenols with antioxidant and anti-inflammatory properties). However, such combinations require careful study for synergism and safety.

Conclusions and future directions

The analysis of the literature data allows us to formulate the following key conclusions. Desialylation of LDL is an early initiating mechanism of atherogenesis that precedes oxidation and triggers a chain of pathological reactions, including macrophage uptake and inflammation. Therefore, inhibition of sialidases represents a promising strategy for the prevention of atherosclerosis at the earliest stages. Natural flavonoids, including gallated catechins, may represent promising candidates for the development of dietary supplements targeting sialidase; however, their efficacy, selectivity, bioavailability, and long-term safety require experimental and clinical validation. Molecular docking is a powerful tool for the primary selection of such compounds, but requires mandatory experimental verification. Previously published docking data indicating high predicted affinity of gallated catechins for sialidase support further investigation of these compounds that can fill the existing niche in the long-term prevention of cardiovascular diseases.

In the future, large randomized clinical trials are needed to confirm the long-term efficacy and safety of the developed compositions. Also relevant are studies on dose optimization, pharmacokinetics, and possible drug interactions. Of particular interest is the search for new sialidase inhibitors among other classes of natural compounds, as well as the study of the effect of combinations on the progression of atherosclerosis, assessed by modern imaging methods (*e.g*., ultrasound of the carotid arteries or coronary CT angiography). Given that atherosclerosis is a systemic disease, influencing its early links may not only slow the development of plaques but also reduce the incidence of acute events. The development of such dietary supplements opens up new horizons for the integration of nutraceutics and cardiology in personalized prevention of cardiovascular diseases.

Declarations

Author contributions: Tatyana Ivanovna Kovyanova: conceptualization, writing–original draft and writing review. Daria Dmitryevna Borodko: formal analysis. Ulyana Vyacheslavovna Rozhkova: validation. Stanislav Anatolievich Antonov: investigation. Aleksandra Sergeevna Utkina: resources. Vasily Petrovich Karagodin: funding acquisition and project administration. Galina Alexandrovna Chizhikova: editing. All authors read and approved the final version of the manuscript.

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