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Review

Natural Bioactive Compounds Targeting the ANGPTL3/4/8 Axis in Dyslipidemia and Cardiometabolic Disease: Molecular Mechanisms, Evidence Hierarchy, and Clinical Translation

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Abstract

Dyslipidemia driven by excess triglyceride-rich lipoproteins (TGRLs) remains a major modifiable determinant of atherosclerotic cardiovascular disease (ASCVD). Over the past decade, the angiopoietin-like protein (ANGPTL) family (specifically ANGPTL3, ANGPTL4, and ANGPTL8) has emerged as a central regulatory axis controlling lipoprotein lipase (LPL) activity and the tissue-specific partitioning of circulating triglycerides. Human genetic studies of loss-of-function variants and the clinical success of biologic ANGPTL3 inhibitors have validated this axis as a therapeutic target, but these agents are costly, parenterally administered, and reserved for severe or refractory dyslipidemia. In parallel, a growing body of preclinical work has identified naturally occurring bioactive compounds, including citrus polymethoxyflavones, dietary polyphenols, marine- and plant-derived fatty acids, royal jelly constituents, and polysaccharides, which can modulate ANGPTL3, ANGPTL4, or ANGPTL8 expression and downstream LPL activity. This review synthesizes the molecular mechanisms by which these compounds engage the ANGPTL3/4/8 axis, situates the supporting evidence within a hierarchy that spans hepatocyte and myocyte cell culture, rodent and non-human primate models, and the scarce available human trials, and contrasts this evidence base against the mature clinical data underpinning pharmacological ANGPTL inhibitors such as evinacumab. We identify liver X receptor alpha (LXRα) and hepatocyte nuclear factor 4 alpha (HNF4α) as proposed transcriptional nodes for structurally diverse natural ligands, noting that no compound has been shown to engage either receptor directly, and that a requirement for the transcription factor has been established by loss-of-function experiment only for HNF4α, in a single compound and cell line, and we discuss translational obstacles including limited oral bioavailability, interspecies dosing discrepancies, and the near-total absence of adequately powered human outcome trials. We conclude that natural bioactive compounds represent a mechanistically plausible but clinically immature adjunctive strategy for modulating the ANGPTL3/4/8 axis, and we outline the preclinical and clinical research priorities required to move this field toward evidence-based application in cardiometabolic disease management.

Keywords: ANGPTL3; ANGPTL4; ANGPTL8; lipoprotein lipase; dyslipidemia; triglycerides; natural bioactive compounds; nutraceuticals; cardiometabolic disease; LXRα; HNF4α

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1. Introduction

Dyslipidemia, characterized by elevated low-density lipoprotein cholesterol (LDL-C), elevated triglycerides, and/or reduced high-density lipoprotein cholesterol (HDL-C), is one of the most prevalent and modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD), the leading cause of death worldwide. While statins, ezetimibe, and PCSK9-directed therapies have substantially improved LDL-C management, residual cardiovascular risk attributable to elevated triglycerides and triglyceride-rich lipoprotein (TGRL) remnants persists even in patients who achieve guideline LDL-C targets [1]. This residual risk has redirected therapeutic attention toward the regulatory machinery governing triglyceride hydrolysis and lipoprotein clearance, and in particular toward lipoprotein lipase (LPL), the rate-limiting enzyme that hydrolyzes triglycerides carried in chylomicrons and very-low-density lipoproteins (VLDLs) at the capillary endothelium [2].

LPL activity is not constitutive: it is dynamically tuned by a family of secreted angiopoietin-like proteins, ANGPTL3, ANGPTL4, and ANGPTL8, which act as endogenous, tissue-selective LPL inhibitors [3,4]. Human genetic evidence has been decisive in validating this axis: individuals carrying loss-of-function variants in ANGPTL3 exhibit familial combined hypolipidemia, characterized by low levels of all major lipoprotein classes, and are afforded substantial protection from coronary artery disease without an adverse compensatory phenotype [5,6]. This genetic proof of concept catalyzed the development of biologic ANGPTL3/4/8-directed therapeutics, including the monoclonal antibody evinacumab (approved for homozygous familial hypercholesterolemia), the antisense oligonucleotide vupanorsen, and RNA-interference agents such as zodasiran, alongside antibodies targeting ANGPTL8 or the ANGPTL3-ANGPTL8 complex [4,7–9]. These agents demonstrate that pharmacological modulation of the ANGPTL axis can markedly lower triglycerides, LDL-C, and apolipoprotein B [4].

Independently of this pharmaceutical trajectory, a parallel and much less consolidated literature has examined whether naturally occurring dietary and phytochemical constituents can engage the same axis. These studies span citrus-derived polymethoxyflavones [10,11], raspberry polyphenols combined with fermentable fibers [12], fatty acid classes from cottonseed oil, fish oil, and whole milk [13–17], royal jelly-derived medium-chain fatty acids [18], marine-derived chitosan [19], and common dietary flavonols such as quercetin [20]. Individually, each study offers a plausible mechanistic link to ANGPTL3, ANGPTL4, or ANGPTL8; collectively, however, the evidence remains fragmented, mechanistically heterogeneous, and almost entirely confined to in vitro and animal models. No dedicated systematic synthesis has organized this literature around the ANGPTL3/4/8 axis specifically, nor situated it against the evidentiary standard set by biologic ANGPTL inhibitors.

This gap mirrors a broader pattern across the natural-bioactive-compound field addressed by the present Special Issue: chronic diseases as diverse as cardiovascular disease, cancer, diabetes, and obesity share a common substrate of sustained oxidative stress and low-grade inflammation, and a substantial body of work has catalogued the capacity of dietary polyphenols, flavonoids, and other phytochemicals to modulate these processes through antioxidant, anti-inflammatory, and redox-signaling mechanisms, including activation of the Nrf2/Keap1/ARE pathway and suppression of NF-κB- and NLRP3 inflammasome-dependent signaling [21–24]. Several of the compounds discussed in this review, most notably flavonoids such as quercetin and dietary polyphenols, belong to these same chemical classes, and nutraceutical strategies that jointly target oxidative stress, inflammation, and lipid metabolism (including leaf-derived phytochemicals shown to lower obesity-associated inflammatory biomarkers such as TNF-α, IL-6, and CRP) have been proposed as a more holistic approach to cardiometabolic risk reduction than single-target agents [25,26]. However, the bioavailability and bioaccessibility limitations that constrain systemic exposure to

ingested phytochemicals in general [27] apply equally to the ANGPTL-modulating compounds reviewed here, reinforcing the pharmacokinetic barriers discussed in Section 5.1.

The present review addresses this synthesis gap. It also extends to cardiometabolic disease an evidence-hierarchy framework that we have applied to natural-compound literatures in age-related endocrine decline [28–30], a population in which triglyceride-rich lipoprotein burden, and therefore the plausible indication for the compounds reviewed below, is greatest. We first summarize the molecular architecture of the ANGPTL3/4/8 axis and its transcriptional control, establishing the mechanistic vocabulary needed to interpret the natural-compound literature. We then review, compound class by compound class, the evidence that specific natural bioactive substances modulate ANGPTL3, ANGPTL4, or ANGPTL8 expression, secretion, or downstream LPL activity, and the lipid-lowering phenotypes reported in association with these effects. We subsequently organize this evidence within a hierarchy (in vitro, animal, and human) and benchmark it against the clinical trial and human genetic data available for biologic ANGPTL inhibitors. Finally, we discuss the translational barriers that currently separate mechanistic promise from clinical application and propose research priorities capable of narrowing that gap.

Literature Identification

Although this is a narrative rather than a systematic review, the basis for its coverage is stated here so that readers can judge it. PubMed/MEDLINE, Scopus, and Web of Science were searched from January 2011 up to June 2026, combining ANGPTL3, ANGPTL4, ANGPTL8, and angiopoietin-like protein with natural compound, polyphenol, flavonoid, nutraceutical, dietary, plant extract, fatty acid, polysaccharide, and individual compound names. Primary studies in any model system were eligible if they reported a direct measurement of ANGPTL3, ANGPTL4, or ANGPTL8 mRNA, protein, or complex levels in response to a natural-compound or dietary intervention; studies reporting lipid endpoints without ANGPTL measurement, non-English publications, and conference abstracts without full data were excluded. Backward and forward citation tracking of eligible articles supplemented the database searches and identified one foundational genetic study published before this window, which was retained. On this basis, we identified no previous review organized specifically around natural-compound modulation of the ANGPTL3/4/8 axis, and no human randomized trial of any reviewed compound with ANGPTL endpoints other than the cottonseed oil trials discussed in Section 3.4.1.

2. Molecular Architecture and Regulation of the Angptl3/4/8 Axis

2.1. Angptl3: A Hepatokine with Endocrine Reach

ANGPTL3 is a ~70 kDa glycoprotein synthesized almost exclusively by hepatocytes and secreted into the circulation as a true endocrine hepatokine [5]. Its N-terminal coiled-coil domain inhibits both LPL and endothelial lipase, while proteolytic cleavage by furin-family proteases (at the R221-R224/T226 site) releases this N-terminal fragment; this cleavage event potentiates ANGPTL3's inhibitory activity against endothelial lipase (EL) more than against LPL, indicating that furin-mediated processing is of particular importance for the EL-inhibitory, rather than the LPL-inhibitory, function of ANGPTL3, while GalNAc-type O-glycosylation further modulates its stability and activity [6]. Unlike ANGPTL4, ANGPTL3 transcription is not acutely responsive to feeding or fasting in the same paracrine sense but is instead regulated by nuclear receptors that sense hepatic lipid and lipoprotein status, principally liver X receptor alpha (LXRα) and hepatocyte nuclear factor 1 alpha (HNF-1α) [6,10]. Because it circulates systemically, hepatic ANGPTL3 can inhibit LPL in tissues distant from the liver, including cardiac and skeletal muscle and adipose tissue, making it a systemic rheostat for triglyceride partitioning [4]. Human loss-of-function

variants in ANGPTL3 cause familial combined hypolipidemia [31] and are associated with an estimated 34–41% lower odds of coronary artery disease [32,33], providing among the strongest genetic validations of any current lipid-lowering target [5,6].

2.2. Angptl4: A Fasting-Induced, Tissue-Autonomous Regulator

In contrast to ANGPTL3, ANGPTL4 is widely expressed across the liver, adipose tissue, skeletal muscle, heart, and intestine and acts predominantly in a paracrine or autocrine manner near its site of synthesis [2,4]. ANGPTL4 is a peroxisome proliferator-activated receptor (PPAR) target gene and is strongly induced by fasting, exercise, cold exposure, and fatty acid flux, coordinating a shift of triglyceride delivery away from peripheral tissues during states of energy scarcity [2]. Mechanistically, ANGPTL4 inhibits LPL by increasing the enzyme's inherent instability, promoting unfolding of its catalytic domain; an earlier dimer-to-monomer model is now considered unlikely because LPL is catalytically active as a monomer, and a reversible, uncompetitive mode of inhibition has also been proposed [4]. In white adipose tissue, locally produced ANGPTL4 suppresses LPL-mediated fatty acid uptake during fasting, redirecting substrate toward oxidative tissues [3]. Angptl4-knockout mice fed a high-saturated-fat diet develop lipid accumulation in mesenteric lymph nodes, systemic inflammation, and chylous ascites, a toxicity not observed with ANGPTL3 inhibition, which initially steered drug development preferentially toward ANGPTL3 and ANGPTL8 rather than ANGPTL4 itself [4]. This signal now appears to be species-dependent. The humanized anti-ANGPTL4 antibody MAR001 lowered plasma triglycerides by up to 58%, non-HDL cholesterol by 38%, apolipoprotein B by 30%, and remnant cholesterol by 59% in hypertriglyceridemic non-human primates and was well tolerated in 15-week subchronic and 9-month chronic toxicology studies, including under sustained high-saturated-fat feeding, with mesenteric lymph node findings limited to foamy macrophage accumulation that did not progress to inflammation, necrosis, or fibrosis [34]. Human ANGPTL4 loss-of-function is likewise associated with lower triglycerides, remnant cholesterol and apolipoprotein B and with reduced risk of type 2 diabetes and ASCVD, without identified safety concerns [35]. ANGPTL4 therefore remains under active clinical investigation, and the murine phenotype should not be assumed to predict outcomes in primates or humans.

2.3. Angptl8: The Feeding-Induced Activating Partner

ANGPTL8 (also known as betatrophin, lipasin, or RIFL) is expressed in the liver and adipose tissue and is induced by feeding, in reciprocal counterpoint to the fasting-induced ANGPTL4 [3]. ANGPTL8 possesses no independent LPL-inhibitory activity; instead, its physiological role is to complex with ANGPTL3 [4]. The resulting ANGPTL3-ANGPTL8 complex, which assembles with an approximate 3:1 stoichiometry, is an LPL inhibitor several orders of magnitude more potent than ANGPTL3 alone, and represents the physiologically dominant inhibitory species during the fed state, when it suppresses LPL in cardiac and skeletal muscle to divert circulating triglyceride toward white adipose tissue for storage [4]. ANGPTL8 can additionally complex with ANGPTL4 in a 1:1 stoichiometry; paradoxically, this ANGPTL4-ANGPTL8 complex has reduced LPL-inhibitory potency relative to ANGPTL4 alone, adding a further layer of context-dependent regulation [4]. Hepatic ANGPTL8 transcription is under the control of hepatocyte nuclear factor 4 alpha (HNF4α), which binds a direct-repeat-1 (DR1)-like element in the proximal ANGPTL8 promoter [18].

2.4. The Integrated 3-4-8 Model of Triglyceride Trafficking

These three proteins operate as an integrated feeding–fasting switch first articulated as the "ANGPTL3-4-8 model" [3] and subsequently refined [4]. During fasting, locally produced ANGPTL4 predominates, inhibiting LPL in white adipose tissue and sparing muscle

and cardiac LPL activity so that circulating triglyceride is directed toward oxidative tissues for energy production [3]. Upon refeeding, hepatic ANGPTL8 is rapidly induced, forms the high-potency complex with circulating ANGPTL3, and this complex selectively inhibits LPL in cardiac and skeletal muscle while sparing adipose LPL, thereby redirecting dietary triglyceride toward adipose storage [3,4]. GPIHBP1, the endothelial glycosylphosphatidylinositol-anchored protein that transports LPL to the luminal surface of capillaries and stabilizes its interaction with lipoprotein substrate, provides the physical platform on which this ANGPTL-mediated inhibition occurs [3]. Because this switch operates tissue-selectively rather than as a uniform systemic brake on lipolysis, natural or pharmacological interventions that alter the relative expression or activity of ANGPTL3, ANGPTL4, or ANGPTL8 can, in principle, be tuned toward specific metabolic outcomes (hepatic triglyceride export, peripheral triglyceride clearance, or adipose fat storage), depending on which node of the axis is engaged.

2.5. Transcriptional Regulators of ANGPTL3 and ANGPTL8: LXRα and HNF4α/HNF-1α

A recurring proposal in the natural-compound literature reviewed below is convergence on a small number of transcriptional regulators of the ANGPTL3 and ANGPTL8 promoters. LXRα, a nuclear receptor activated by oxysterols and a master regulator of hepatic lipid and cholesterol homeostasis, transactivates the ANGPTL3 promoter, and pharmacological or phytochemical antagonism of LXRα activation has been proposed to suppress ANGPTL3 transcription and secretion in hepatocyte models [10,11]. HNF4α, a master regulator of hepatocyte identity and metabolic gene expression, occupies a DR1-like element in the ANGPTL8 promoter, and its abundance and promoter occupancy are rate-limiting for ANGPTL8 transcription; compounds that reduce nuclear HNF4α protein correspondingly suppress ANGPTL8 expression [18]. These two regulators are invoked for several of the structurally unrelated compounds discussed in Section 3, but the supporting evidence is uneven. HNF4α dependence has been confirmed by knockdown for one compound in one cell line, whereas LXRα dependence has not been tested by loss-of-function methods for any compound. Convergence on a limited set of druggable transcriptional intermediates is therefore a hypothesis generated by a small number of studies rather than an established property of this literature, and the compounds with the most robust human ANGPTL data, the dietary fatty acids, have no identified transcriptional mechanism at all. This tissue-selective regulatory logic across the feeding–fasting cycle is summarized in Figure 1, and the comparative structural and functional biology of the three paralogues is summarized in Table 1.

Table 1. Comparative biology of ANGPTL3, ANGPTL4, and ANGPTL8.

Feature	ANGPTL3	ANGPTL4	ANGPTL8
Tissue of origin	Liver (hepatocytes)	Liver, adipose, muscle, heart, intestine	Liver and adipose tissue
Mode of action	Endocrine (systemic)	Paracrine/autocrine (local)	Endocrine/paracrine (as ANGPTL3 partner)
Feeding regulation	Not acutely feeding-regulated	Induced by fasting, exercise, cold	Induced by feeding

Table 1. *Cont.*

Feature	ANGPTL3	ANGPTL4	ANGPTL8
LPL-inhibition mechanism	Inhibition reported as reversible and non-catalytic, though unfolding of LPL has also been proposed; requires ANGPTL8 for maximal potency	Destabilization and unfolding of the LPL catalytic domain	No independent LPL-inhibitory activity
Key molecular partner	ANGPTL8 (3:1 complex; high-potency LPL inhibitor)	ANGPTL8 (1:1 complex; reduces ANGPTL4 potency)	ANGPTL3 (activates); ANGPTL4 (attenuates)
Transcriptional regulator	LXRα, HNF-1α	PPAR family	HNF4α
Physiological role	Fed-state redirection of TG to adipose (via complex)	Fasted-state redirection of TG to oxidative tissue	Feeding-induced activator of ANGPTL3
Human genetic/drug validation	LOF variants → familial combined hypolipidemia, ↓ CAD risk; target of evinacumab, vupanorsen, zodasiran	LOF variants → ↓ TG, ↓ remnant-C, ↓ T2D and ASCVD risk; murine KO toxicity not reproduced in primates (MAR001)	Target of emerging ANGPTL8/complex-directed antibodies

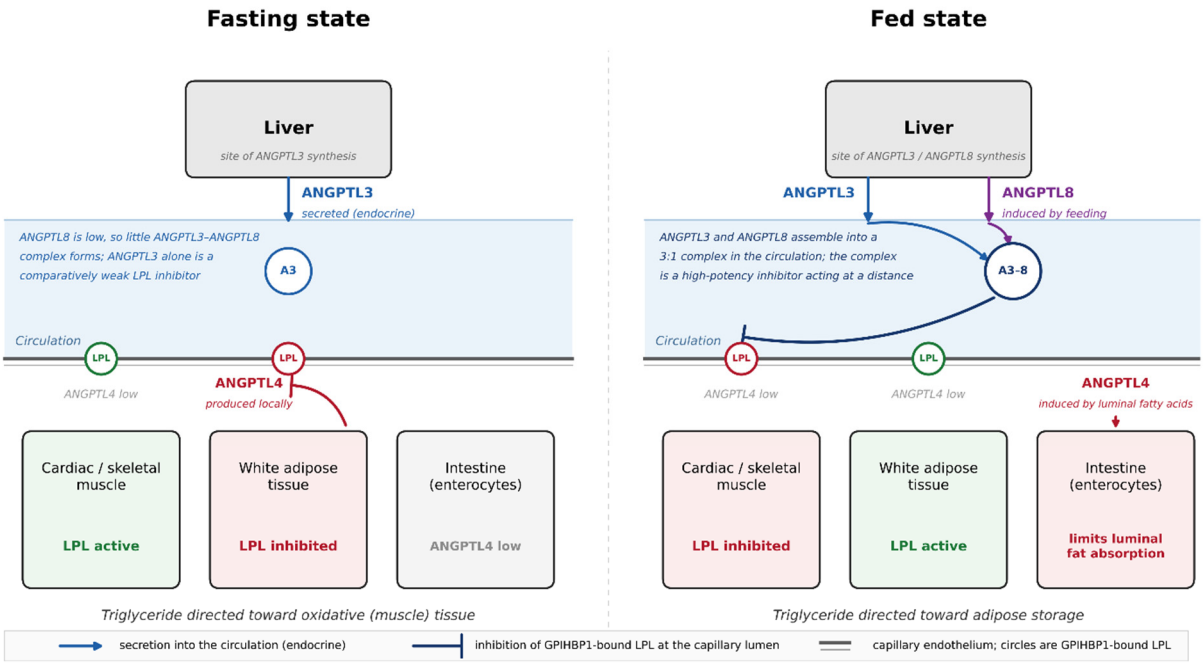


Figure 1. Tissue-selective regulation of lipoprotein lipase by the ANGPTL3/4/8 axis across the feeding–fasting cycle. Fasted (left) and fed (right) states. The liver sits above the circulation (shaded band), separated from the peripheral tissues by the capillary endothelium (double line); circles on the endothelium are GPIHBP1-bound LPL, green when active and red when inhibited. Arrows with a solid head denote secretion into the circulation; lines ending in a bar denote LPL inhibition. Each arrow runs from the site of synthesis to the site of action, so endocrine action (ANGPTL3 and the ANGPTL3–ANGPTL8 complex, liver to distant capillary) is distinguished from paracrine action (ANGPTL4, within one tissue). Intestinal ANGPTL4 limits luminal fatty acid absorption and so carries no capillary LPL symbol. Established physiology [3,4]; proposed mechanisms of compound action are shown in Figure 2. Abbreviations: A3, ANGPTL3; A3–8, ANGPTL3–ANGPTL8 complex; ANGPTL, angiopoietin-like protein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LPL, lipoprotein lipase.

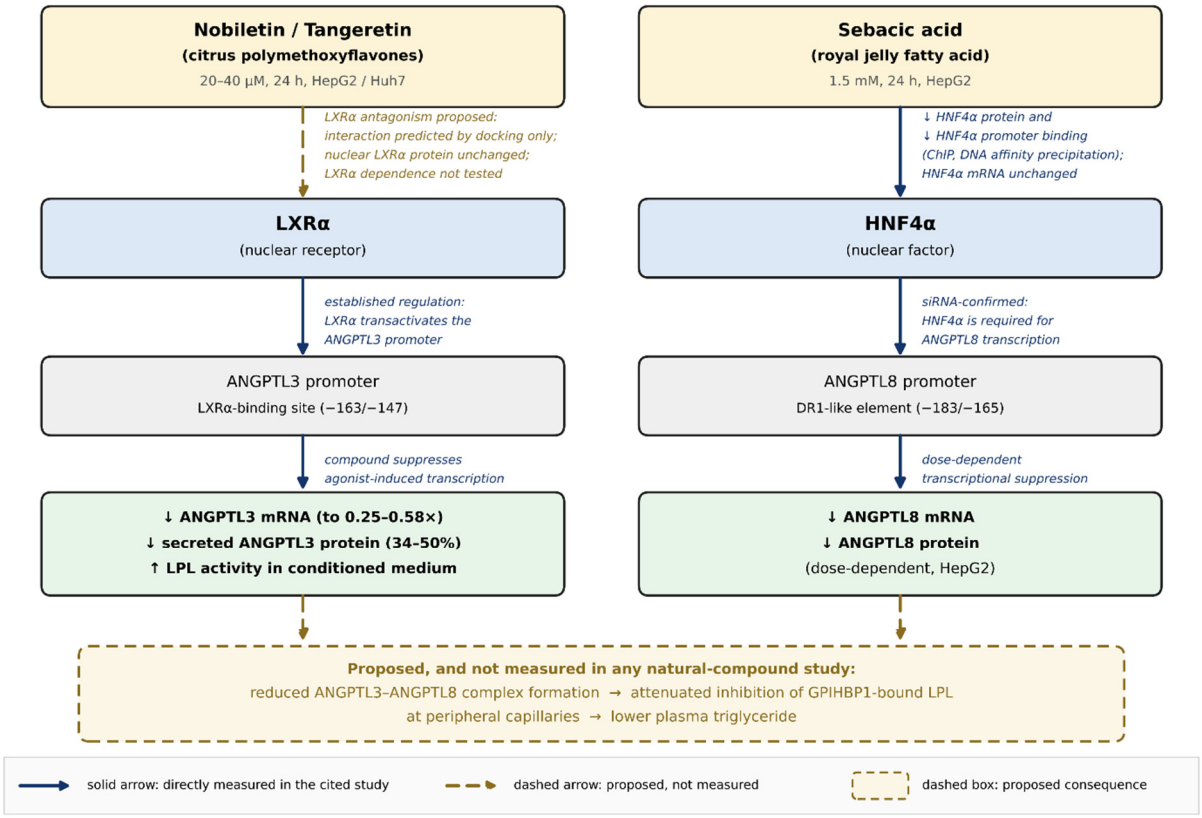


Figure 2. Proposed transcriptional nodes through which natural bioactive compounds modulate the ANGPTL3/4/8 axis. Solid arrows denote relationships directly measured in the cited studies; dashed arrows denote proposed steps that were not measured; the dashed box marks a proposed downstream consequence. The two limbs differ in evidential strength. For the citrus flavones, suppression of agonist-induced *ANGPTL3* transcription was measured, but LXRα engagement was not: the interaction was a docking prediction, nuclear LXRα protein was unchanged, and dependence was untested [10,11]. For sebacic acid, reduced HNF4α protein and promoter occupancy were measured, and the requirement for HNF4α was siRNA-confirmed [18]. The step by which sebacic acid lowers HNF4α protein was not identified, so the compound's proximal target is unknown; the solid arrows denote measured relationships, not demonstrated binding. Neither reduced ANGPTL3–ANGPTL8 complex formation nor attenuated peripheral LPL inhibition was measured in any natural-compound study. These nodes are not a general mechanism: the dietary fatty acids, which supply the only human data here, have no identified transcriptional mechanism. Abbreviations: ANGPTL, angiopoietin-like protein; DR1, direct repeat 1; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HNF4α, hepatocyte nuclear factor 4 alpha; LPL, lipoprotein lipase; LXRα, liver X receptor alpha; siRNA, small interfering RNA.

3. Natural Bioactive Compounds Modulating the Angptl3/4/8 Axis

This section reviews, compound by compound, the natural bioactive substances shown to modulate ANGPTL3, ANGPTL4, or ANGPTL8, organized according to the convergent transcriptional mechanisms summarized in Figure 2.

3.1. Citrus Polymethoxyflavones: Evidence and Mechanistic Uncertainty

Nobiletin and tangeretin are polymethoxylated flavones enriched in citrus peel that have independently been reported to suppress hepatic ANGPTL3 expression, with LXRα proposed as the mediating node [10,11]. In HepG2 and Huh7 hepatocyte lines, nobiletin (20–40 μM) reduced ANGPTL3 mRNA to approximately 0.25–0.40-fold of control and reduced secreted ANGPTL3 protein by approximately 49.7%, with a corresponding 1.7-fold

restoration of extracellular LPL activity [10]. In adult zebrafish maintained on a high-fat diet, nobiletin administration reduced plasma triglycerides by approximately 21% and total cholesterol by approximately 16% [10]. Molecular docking indicated that nobiletin occupies the LXRα ligand-binding domain (docking score −8.17 kcal/mol), forming π-π stacking interactions with Phe315, which the authors interpreted as an LXRα-antagonist-like mode of action. These docking data are computational predictions rather than measurements of binding. Nuclear LXRα protein was unchanged by nobiletin, and no ligand-binding assay, competitive displacement assay, or LXRα knockdown was performed, so LXRα dependence remains untested; what was demonstrated functionally is suppression of T0901317-induced ANGPTL3 promoter activity and mRNA in a reporter assay [10]. The in vivo LPL measurement was made on liver lysates from adult male zebrafish rather than at the peripheral capillary endothelium [10]. Tangeretin produced parallel effects in the same hepatocyte models: ANGPTL3 mRNA fell to approximately 0.37–0.58-fold of control in HepG2 cells, secreted ANGPTL3 protein decreased by 34–47%, and extracellular LPL activity rose to approximately 217% of control [11]. Tangeretin's predicted LXRα-binding docking score (−8.64 kcal/mol) approached that of the synthetic LXR agonist T0901317 (−8.71 kcal/mol) used as the reference ligand, although nuclear LXRα and HNF-1α protein levels were likewise unchanged by tangeretin, and LXRα dependence was not tested, so the shared target remains proposed rather than established [11]. Together, these two structurally related citrus flavonoids constitute the most detailed transcriptional evidence in the natural-compound literature for suppression of ANGPTL3 expression, although receptor-level engagement remains unconfirmed, both studies remain confined to hepatocyte culture and a single lower-vertebrate in vivo model, and neither has been evaluated in mammalian models or humans.

3.2. Raspberry Polyphenols Combined with Fermentable Fiber: Angptl4 Suppression in Hepatic Steatosis

Raspberry-derived polyphenols, principally ellagitannins and anthocyanins, have been evaluated in combination with fermentable dietary fibers (fructo-oligosaccharides, FOS, or pectin) in a rat model of diet-induced nonalcoholic fatty liver [12]. Among the tested combinations, raspberry extract combined with FOS produced the greatest reductions in plasma triglycerides and hepatic cholesterol, triglyceride, and fat content, alongside decreased hepatic Angptl4 and PPARγ mRNA [12]. The accompanying markers reflect distinct processes and are reported here separately: plasma interleukin-6, a circulating pro-inflammatory cytokine, plasma aspartate aminotransferase activity, a marker of hepatocellular injury, and hepatic malondialdehyde, a marker of lipid peroxidation, were each reduced, with less lobular and portal inflammatory cell infiltration on histology, while plasma alanine aminotransferase and alkaline phosphatase were unchanged [12]. ANGPTL4 was measured as hepatic mRNA only, not in the intestine, plasma, or at the protein level, and the feeding state at sampling was not reported. Cecal short-chain fatty acid production was measured directly in the same animals and was reduced, not increased, by the raspberry extract and fructo-oligosaccharide combination, so a microbiota-derived short-chain fatty acid signal to hepatic ANGPTL4 is not supported by the fermentation data; no step linking microbial metabolites to hepatic ANGPTL4 was experimentally isolated [12]. The study compared four dietary groups without a fiber-only arm and without a formal test of interaction, so the larger response to the combination cannot be distinguished from additivity, and the independent contribution of the fiber cannot be determined.

3.3. Royal Jelly-Derived Sebacic Acid: Hnf4α-Mediated Suppression of Angptl8

Among the medium-chain and dicarboxylic fatty acids present in royal jelly (10-hydroxy-2-decenoic acid, 10H2DA; 10-hydroxydecanoic acid, 10HDA; and sebacic acid, SA), sebacic acid emerged as the most potent suppressor of ANGPTL8 in HepG2 hepatocytes, producing a dose-dependent reduction in both ANGPTL8 mRNA and protein at concentrations up to 1.5 mM [18]. Mechanistically, sebacic acid decreased HNF4α protein levels and thereby reduced binding of HNF4α to a newly identified HNF4α response element located at position −183/−165 of the ANGPTL8 promoter, a DR1-like motif; small interfering RNA-mediated knockdown of HNF4α reproduced the suppressive effect on ANGPTL8 and confirmed HNF4α as the necessary transcriptional intermediate [18]. This study provides the only account in the reviewed literature in which the requirement for the implicated transcription factor was tested directly, although the step linking the compound to the loss of HNF4α protein remains unidentified. It parallels the LXRα–ANGPTL3 mechanism proposed, but not confirmed by a loss-of-function experiment, for the citrus flavonoids [10,11], and illustrates that different classes of natural lipophilic compounds may selectively engage distinct nodes of the ANGPTL3/4/8 network. Two qualifications temper this account. Sebacic acid did not alter HNF4α mRNA, so the authors infer accelerated protein degradation by a mechanism that remains unidentified, and the effective millimolar concentration is roughly two orders of magnitude above the micromolar range used for the citrus flavones. Furthermore, HNF4α is a master regulator of hepatocyte identity governing gluconeogenic, bile acid, urea cycle, apolipoprotein, and drug-metabolizing gene programs, and its hepatic loss produces steatosis and impaired VLDL secretion in model systems, while HNF4A variants cause maturity-onset diabetes of the young. The cited study assessed no HNF4α target gene other than ANGPTL8 and no broader metabolic readout, and was conducted exclusively in HepG2 cells without in vivo confirmation [18]. Reduction of a pleiotropic regulator cannot therefore be assumed beneficial on the basis of its effect on a single downstream gene.

3.4. Dietary Fatty Acids and Oils

3.4.1. Cottonseed Oil

Cottonseed oil (CSO), rich in linoleic acid, has been evaluated in the only body of human randomized controlled trial (RCT) evidence directly linking a natural dietary fat to circulating ANGPTL protein concentrations [13,14]. A systematic review identified two eligible trials (three publications) comparing CSO to olive oil (OO) [36]. Short-term feeding (5 days) with CSO produced lower LDL-C and triglycerides than OO; longer-term feeding (56 days) produced lower total cholesterol, LDL-C, non-HDL-C, and apolipoprotein B [36,37]. Critically, in the same crossover participants (15 healthy normal-weight men), postprandial ANGPTL3, ANGPTL4, and ANGPTL8 concentrations decreased after the CSO diet while increasing after the OO diet, and fasting ANGPTL3, ANGPTL4, and ANGPTL8 increased after OO with no significant change after CSO [14]. A subsequent secondary analysis of an 8-week parallel-arm RCT in hypercholesterolemic adults ($n = 42$, 37% male) found treatment-by-visit interactions for postprandial ANGPTL3 and ANGPTL4 that reflected increases in the OO arm rather than decreases in the CSO arm, with no difference for ANGPTL8; fasting ANGPTL3 tended to increase in the CSO arm ($p = 0.06$) [15]. The ANGPTL benefit attributed to cottonseed oil is therefore relative to olive oil rather than an absolute reduction, a distinction that matters when these data are read as evidence of active ANGPTL suppression. This cottonseed oil literature is unique in the present review as the only natural-compound evidence with direct, quantitative human ANGPTL measurements from randomized, controlled feeding trials, and as such occupies the highest position in the evidence hierarchy discussed in Section 4.

3.4.2. Fish Oil/Omega-3 Fatty Acids

In rhesus macaques, a high-fructose diet increased circulating ANGPTL3 by 30–40%, an increase best explained by the concurrent development of fasting hyperinsulinemia and higher HOMA-IR [16]. Co-administration of fish oil prevented this fructose-induced rise in ANGPTL3, demonstrating that omega-3 fatty acids can counteract diet-induced ANGPTL3 induction in a translationally relevant non-human primate model, but did not attenuate the parallel increases in plasma C-reactive protein and interleukin-6, indicating that the effect on ANGPTL3 is independent of systemic inflammation rather than a manifestation of it [16]. In the same study, direct RNA interference-mediated knockdown of ANGPTL3 (ARO-ANGPTL3) reduced circulating ANGPTL3 by more than 90% and produced reductions of approximately 80% in triglycerides and 50% in total cholesterol, together with reductions of approximately 50% in HDL-C and 40% in apolipoprotein A1, providing an internal pharmacological benchmark within the same model system against which the more modest, preventive effect of fish oil can be calibrated [16].

3.4.3. A-Linolenic Acid Versus Linoleic Acid

In obese Zucker rats, skeletal muscle Angptl4 expression was elevated in all obese groups, but dietary supplementation with the omega-3 essential fatty acid α-linolenic acid (ALA) significantly blunted this increase relative to both a standard (AIN-93G) obese control diet and a linoleic acid (LA, omega-6, from safflower oil)-supplemented diet, and lowered ANGPTL4 protein in non-fasted serum; muscle Angptl4 was measured as mRNA in red tibialis anterior [38]. In a complementary in vitro experiment using differentiated L6 myotubes, ALA (200 μM) reduced ANGPTL4 protein in the secretion medium, consistent in direction with its effect in vivo [38]. These findings suggest that the balance of dietary omega-3 to omega-6 polyunsaturated fatty acids, rather than total polyunsaturated fatty acid intake alone, may differentially tune skeletal muscle ANGPTL4 expression and, by extension, local LPL activity and muscle triglyceride uptake.

3.4.4. Whole Milk Fatty Acids

In a porcine model, whole milk feeding increased intestinal ANGPTL4 mRNA expression, and short- and medium-chain free fatty acids (C4-C8) were shown in Ussing chamber and Caco-2 cell models to directly induce ANGPTL4 expression in intestinal epithelium [17]. Whole milk feeding was additionally associated with increased fecal free fatty acid and urinary organic acid excretion, suggesting that milk fat-derived short/medium-chain fatty acids induce intestinal ANGPTL4 as part of a broader adaptation that limits fatty acid absorption, an effect that, unlike the hepatic and myocyte mechanisms above, is localized to the gut epithelium [17].

3.5. Chitosan: A Polysaccharide Modulator of Intestinal and Hepatic Angptl4

Chitosan, a deacetylated marine-derived polysaccharide available in high- and low-molecular-weight forms, has been shown in high-fat diet-fed rats to reverse the diet-induced suppression of ANGPTL4 protein in blood and intestine, measured by Western blot, and of hepatic microsomal triglyceride transfer protein (MTTP) and apolipoprotein E; hepatic ANGPTL4 was not measured, and animals were fasted for 12 h before sampling [19]. Both chitosan preparations, and high-molecular-weight chitosan more markedly, increased fecal lipid excretion, activated hepatic AMP-activated protein kinase (AMPK) and PPARα signaling, and suppressed SREBP-1c, SREBP-2, and PPARγ expression [19]. High-molecular-weight chitosan also reduced triglyceride content and LPL activity and increased the lipolysis rate in perirenal adipose tissue, so the rise in intestinal and circulating ANGPTL4 was accompanied by lower, not higher, LPL activity in the one peripheral tissue where

that activity was measured [19]. The restoration of ANGPTL4 expression toward normal (chow-fed) levels, rather than its suppression, distinguishes chitosan mechanistically from the ANGPTL3/ANGPTL8-suppressing compounds discussed above: here, the therapeutic direction of effect is the correction of diet-induced ANGPTL4 deficiency rather than the induction of a supraphysiological suppression, illustrating that "beneficial" modulation of the ANGPTL axis is context-dependent and baseline-dependent rather than uniformly directional. These directionally opposite findings are in any case not directly comparable. The raspberry polyphenol study measured hepatic Angptl4 mRNA against an untreated obesogenic-diet control, whereas the chitosan study measured ANGPTL4 protein in blood and intestine, in fasted animals, against both high-fat and normal-control groups; tissue mRNA and circulating protein are not equivalent measures. Because ANGPTL4 acts predominantly in a paracrine manner, hepatic suppression and intestinal restoration do not lie on a single beneficial-to-harmful axis. Suppression of hepatic ANGPTL4 would be expected to relieve local inhibition of hepatic LPL; intestinal ANGPTL4 induction acts on dietary lipid entry rather than on plasma triglyceride hydrolysis, consistent with the increased fecal lipid and fatty acid excretion reported with both chitosan and whole milk feeding; and reduced skeletal muscle ANGPTL4 would be expected to raise local LPL activity and muscle triglyceride uptake, which could in principle promote intramyocellular lipid accumulation. None of these interpretations has been tested, because no study paired an ANGPTL4 measurement with LPL activity in the same tissue, and the physiological significance of the opposing responses therefore remains unresolved.

3.6. Quercetin: Triglyceride Lowering Without Detectable Change in Adipose Angptl4

Quercetin, one of the most extensively studied dietary flavonols, lowered plasma triglycerides by approximately 19% in high-fat-diet-fed mice through a 13% reduction in hepatic apolipoprotein B (Apob) expression, which the authors describe as suggesting rather than demonstrating reduced VLDL production, and through browning of subcutaneous white adipose tissue, evidenced by marked induction of uncoupling protein 1 (Ucp1, +229%) and Elovl3 (+138%) [20]. Direct kinetic measurement with glycerol tri [3H]oleate-labelled lipoprotein-like particles showed a selective 60% increase in uptake of triglyceride-derived fatty acids by subcutaneous white adipose tissue, with no change in the other adipose depots, skeletal muscle, or liver; this is the only direct measurement of tissue lipid uptake in the literature reviewed here [20]. Notably, and in contrast to the assumption that flavonoid-mediated triglyceride lowering routinely operates through the ANGPTL axis, quercetin produced no significant change in Angptl4 expression in subcutaneous white, brown, gonadal, or visceral adipose tissue depots [20]. This negative result supports a narrower conclusion than ANGPTL independence. Angptl4 was measured in adipose depots only, alongside Lpl and Cd36, which were likewise unchanged, while hepatic, skeletal muscle, and intestinal Angptl4, ANGPTL4 protein, ANGPTL3, ANGPTL8, complex formation, and LPL activity were not assessed, so involvement of the axis cannot be excluded. The mechanisms that were demonstrated are nonetheless sufficient to account for the observed triglyceride reduction without invoking it, and the finding cautions against assuming that any polyphenol with lipid-lowering activity necessarily acts through ANGPTL3, ANGPTL4, or ANGPTL8 without direct mechanistic confirmation. The natural bioactive compounds reviewed in this section, together with their reported effects on the ANGPTL3/4/8 axis, are summarized in Table 2.

Table 2. Summary of natural bioactive compounds reported to modulate the ANGPTL3/4/8 axis.

Compound	Model System	Dose/Exposure	ANGPTL Target	Key Effect	Reference
Nobiletin	HepG2/Huh7 ($n = 3$); adult male HFD zebrafish	20–40 μM, 24 h (cells)	ANGPTL3 ↓ (LXRα proposed, unconfirmed)	Cell mRNA to 0.25–0.40×; secreted protein ↓ 49.7%; LPL activity ×1.7 (conditioned medium); plasma TG ↓ 21%, TC ↓ 16% (zebrafish; LPL assayed on liver lysates)	[10]
Tangeretin	HepG2/Huh7 ($n = 3$)	20–40 μM, 24 h	ANGPTL3 ↓ (LXRα proposed, unconfirmed)	Cell mRNA to 0.37–0.58×; secreted protein ↓ 34–47%; LPL activity to 217% (conditioned medium)	[11]
Raspberry polyphenols + FOS	Rat NAFL model, $n = 8$/group	Dietary extract + 3% FOS; feeding state at sampling not reported	Hepatic Angptl4 mRNA ↓ (with PPARγ)	Greatest ↓ plasma TG, hepatic cholesterol/TG/fat; ↓ plasma IL-6 and AST, ↓ hepatic MDA; cecal SCFA also ↓	[12]
Sebacic acid (royal jelly)	HepG2	Up to 1.5 mM, 24 h	ANGPTL8 ↓ (HNF4α-dependent; siRNA-confirmed. Compound target unidentified)	↓ ANGPTL8 mRNA/protein; ↓ HNF4α protein and its binding at −183/−165; confirmed by HNF4α siRNA	[18]
Cottonseed oil	Human RCTs: 15 healthy men (crossover); 42 adults, 37% male (parallel)	Dietary, 5 days/ 8 weeks	ANGPTL3, ANGPTL4, ANGPTL8 (circulating protein)	Postprandial ANGPTL3/4 lower than olive oil, reflecting ↑ in the OO arm rather than ↓ in CSO; ↓ LDL-C, TC, non-HDL-C, apoB; no ANGPTL8 difference at 8 weeks	[14,15]
Fish oil	Adult male rhesus macaque ($n = 10$ vs. 9)	4 g/day, 6 months	Circulating ANGPTL3 (prevents ↑)	Prevented fructose-induced ANGPTL3 rise without attenuating ↑ CRP or ↑ IL-6; benchmarked vs. ARO-ANGPTL3 (>90% ↓)	[16]
α-Linolenic acid (ALA)	Male obese Zucker rats, $n = 8$/group; L6 myotubes	12 weeks, pair-fed; 200 μM (cells)	Angptl4 ↓ (red tibialis anterior mRNA; non-fasted serum protein)	Blunted obesity-induced ↑ in skeletal muscle Angptl4 mRNA; ↓ serum protein vs. LA/standard control diet; ALA ↓ ANGPTL4 secretion from L6 myotubes	[38]
Whole milk fatty acids	Pigs, $n = 9$; Caco-2/Ussing chamber	Dietary; C4–C8 FFAs	Intestinal ANGPTL4 ↑ (mRNA; Caco-2 protein secretion)	↑ intestinal ANGPTL4 mRNA; ↑ fecal FFA and urinary organic acid excretion	[17]
Chitosan (high/low MW)	Male Sprague-Dawley rats, $n = 8$/group	5% chitosan (740 or 91 kDa), 8 weeks, 12 h fasted	ANGPTL4 protein restored (blood, intestine; liver not measured)	Reversed HFD-induced ↓ ANGPTL4; ↑ fecal lipid excretion; AMPK/PPARα ↑, SREBP-1c/2, PPARγ ↓; adipose LPL activity ↓	[19]
Quercetin	Male C57Bl/6J mice, $n = 8$–10	0.1% w/w, 12 weeks (45% fat)	Adipose Angptl4 unchanged; other tissues and paralogues not assessed	↓ plasma TG ~19%; ↓ Apob 13%; sWAT browning (Ucp1 +229%) with +60% TG-derived FA uptake; Angptl4 unchanged in the fat depots examined	[20]

4. Evidence Hierarchy: From Molecular Targets to Clinical Data

The natural-compound literature summarized above spans a wide range of methodological rigor, and interpreting its clinical relevance requires explicit attention to the level of evidence each finding represents. We organize this evidence into three tiers (in vitro, in vivo animal, and human clinical) and then benchmark the aggregate natural-compound evidence base against the substantially more mature evidentiary record supporting biologic ANGPTL3/4/8-directed pharmacotherapy.

4.1. In Vitro Evidence

The most mechanistically resolved data in this field derive from hepatocyte cell line studies (principally HepG2 and Huh7), which have established that nobiletin and tangeretin suppress ANGPTL3 transcription and secretion, with LXRα proposed as the mediating node based on reporter and docking evidence, but not confirmed by loss-of-function experiments [10,11], and that sebacic acid suppresses ANGPTL8 transcription via reduced HNF4α promoter occupancy [18]. These studies benefit from precise molecular dissection, including transcription factor knockdown, promoter mapping, and molecular docking, but are inherently limited by the absence of systemic feeding–fasting cues, immune and endocrine crosstalk, and interspecies differences between human hepatoma lines and native human hepatocytes.

4.2. In Vivo Animal Evidence

A larger set of studies has assessed whole-organism phenotypes in zebrafish given nobiletin [10], rats given raspberry polyphenols with FOS/pectin in a NAFLD model, ALA versus LA, or chitosan [12,19,38], pigs given whole milk fatty acids [17], and, most translationally relevant, rhesus macaques given fish oil against fructose-induced ANGPTL3 elevation, benchmarked against ANGPTL3 RNA interference [16]. These models demonstrate that ANGPTL modulation by natural compounds can translate into measurable changes in circulating or tissue triglycerides, cholesterol, and hepatic steatosis, and the non-human primate fish oil data in particular offer a physiologically relevant intermediate step between rodent findings and human application. However, species-specific differences in lipid metabolism, dosing that often exceeds achievable human dietary intake, and the absence of cardiovascular outcome endpoints in any animal study limit direct extrapolation to human disease. Tissue-level outcomes were reported unevenly across these studies: hepatic lipid content and histology for the raspberry polyphenol and chitosan models, adipose triglyceride content, LPL activity, and lipolysis rate for chitosan, and direct uptake of triglyceride-derived fatty acids across adipose depots, muscle, and liver for quercetin, whereas lipid uptake and accumulation were not assessed for nobiletin, tangeretin, sebacic acid, cottonseed oil, ALA versus LA, or whole milk fatty acids, and insulin sensitivity was measured directly in none of them. Because this axis redistributes rather than simply reduces triglyceride flux, a fall in plasma triglycerides is compatible with increased storage in one or more peripheral depots, and the net effect of most of these compounds on tissue lipid handling therefore remains uncertain.

4.3. Human Clinical Evidence

Human data are markedly sparse and are essentially confined to the cottonseed oil literature, comprising two RCTs assessing postprandial and short-to-medium-term (5- to 56-day, and 8-week) lipid and ANGPTL responses [13–15,37]. Circulating ANGPTL3, ANGPTL4, and ANGPTL8 were measured directly in the companion analyses of these two trials [14,15], which found consistent attenuation of postprandial ANGPTL3/ANGPTL4 responses with cottonseed oil relative to olive oil, while the primary reports of the same trials documented conventional lipid panel improvements [13,37]. No RCT data exist for nobiletin, tangeretin, raspberry polyphenols, royal jelly fatty acids, ALA/LA supplementation, whole milk fatty acids, chitosan, or quercetin with respect to ANGPTL endpoints specifically, and none of the reviewed natural-compound studies, including the cottonseed oil trials, were powered for cardiovascular outcomes, were of long duration, or enrolled populations reflective of the severe dyslipidemias for which pharmacological ANGPTL inhibitors are indicated. Figure 3 depicts the resulting evidence hierarchy, and Table 3 stratifies each natural compound and pharmacological agent discussed in this review by evidentiary tier.

Table 3 and Figure 3 additionally distinguish which class of outcome was measured in each case, since the model system alone conflates studies that quantified ANGPTL levels, LPL activity, and lipid endpoints with those that reported only one of these. Measurements of LPL activity in this literature are limited to conditioned hepatocyte culture medium, zebrafish liver lysates, and adipose tissue in the chitosan study; no study measured LPL activity at the capillary endothelium of a peripheral tissue, none measured ANGPTL3-ANGPTL8 or ANGPTL4-ANGPTL8 complex formation, and for no natural compound has a causal role for ANGPTL modulation in the observed lipid change been experimentally tested.

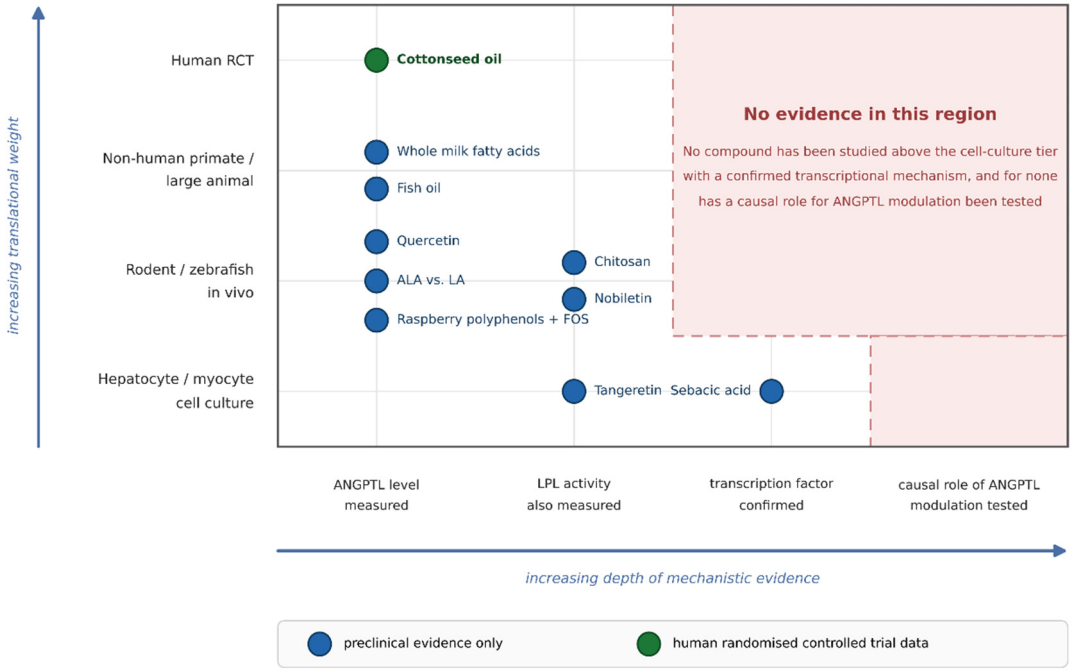


Figure 3. Evidence map for natural bioactive compounds acting on the ANGPTL3/4/8 axis. Each compound is plotted once, at its highest model tier (vertical) and its deepest confirmed mechanistic step (horizontal). The shaded region is empty: no compound has been studied above the cell-culture tier with a confirmed transcriptional mechanism, and for none has a causal role for ANGPTL modulation in the observed lipid change been tested. The distribution is inverse, in that the only compound with human trial data has no identified mechanism, while the only compound with an siRNA-confirmed mechanism has been studied solely in HepG2 cells without an LPL or lipid endpoint. LXRα is proposed but untested for the citrus flavones, so nobiletin and tangeretin are not placed at the transcription-factor level. Which outcome each study measured is given in Table 3, together with the analyte and tissue in each case. Abbreviations: ALA, α-linolenic acid; ANGPTL, angiopoietin-like protein; FOS, fructo-oligosaccharide; LA, linoleic acid; LPL, lipoprotein lipase; LXRα, liver X receptor alpha; RCT, randomized controlled trial.

Table 3. Evidence-tier and outcome matrix for natural compounds and pharmacological agents acting on the ANGPTL3/4/8 axis.

Compound/Agent	Highest Model Tier	ANGPTL Measured (Analyte, Tissue)	LPL Activity Measured (Site)	Lipid/Clinical Endpoint Measured	Causal Role of ANGPTL Modulation Tested
Nobiletin	Animal (zebrafish) + in vitro (HepG2/Huh7)	ANGPTL3 mRNA and secreted protein, hepatocyte culture	Yes—conditioned medium; zebrafish liver lysate. Not at capillary endothelium	Yes—plasma TG ↓ ~21%, TC ↓ ~16% (zebrafish)	No

Table 3. *Cont.*

Compound/Agent	Highest Model Tier	ANGPTL Measured (Analyte, Tissue)	LPL Activity Measured (Site)	Lipid/Clinical Endpoint Measured	Causal Role of ANGPTL Modulation Tested
Tangeretin	In vitro (HepG2/Huh7)	ANGPTL3 mRNA and secreted protein, hepatocyte culture	Yes—conditioned medium only	No	No
Raspberry polyphenols + FOS	Animal (rat)	Angptl4 mRNA, liver only	No	Yes—plasma TG, hepatic cholesterol/TG/fat, histology	No
Sebacic acid (royal jelly)	In vitro (HepG2)	ANGPTL8 mRNA and protein, hepatocyte culture	No	No	No (HNF4α requirement tested; ANGPTL8 → lipid link not tested)
Cottonseed oil	Human RCT (2 trials)	ANGPTL3, ANGPTL4, ANGPTL8 protein, plasma (fasting and postprandial)	No	Yes—LDL-C, TC, non-HDL-C, apoB, TG	No
Fish oil	Animal (rhesus macaque)	ANGPTL3 protein, plasma	No	Yes—plasma lipids; CRP, IL-6, HOMA-IR	No
α-Linolenic acid vs. linoleic acid	Animal (Zucker rat) + in vitro (L6 myotubes)	Angptl4 mRNA, red tibialis anterior; ANGPTL4 protein, non-fasted serum, and myotube medium	No	Not reported	No
Whole milk fatty acids	Animal (pig) + in vitro (Caco-2, Ussing chamber)	ANGPTL4 mRNA, intestine; protein secretion, Caco-2	No	Partial—fecal FFA and urinary organic acid excretion; plasma lipids not reported	No
Chitosan (high/low MW)	Animal (rat)	ANGPTL4 protein, blood and intestine. Liver not measured	Yes—perirenal adipose tissue	Yes—plasma and hepatic lipids, fecal lipid excretion, adipose TG, lipolysis rate	No
Quercetin	Animal (mouse)	Angptl4 mRNA, four adipose depots only (unchanged)	No (Lpl mRNA only)	Yes—plasma TG ↓ ~19%; tissue uptake of TG-derived fatty acid	No
Evinacumab (anti-ANGPTL3 mAb)	Human, phase 3 (approved)	Target engagement by design	No	Yes—TG, LDL-C, HDL-C; approved indication	Target-specific agent: ANGPTL3 inhibition is the intervention
Vupanorsen (ASO)	Human, phase 2b (discontinued)	Hepatic ANGPTL3 knockdown; circulating ANGPTL3	No	Yes—non-HDL-C, TG; hepatic fat, transaminases	Target-specific agent
Zodasiran (siRNA)	Human, phase 2b (phase 3 ongoing)	Circulating ANGPTL3 ↓ up to 74%	No	Yes—TG ↓ up to 63%, lipid panel	Target-specific agent

Note 1. Human loss-of-function genetic evidence validates ANGPTL3 and ANGPTL4 as molecular targets rather than individual compounds or agents, and applies equally to every intervention engaging those targets, including those with no efficacy data of their own; it is therefore discussed separately in Section 4.4 rather than shown agent by agent here. Note 2. "Causal role tested" denotes an experiment in which ANGPTL modulation was blocked or bypassed (for example, by knockdown, knockout, or receptor-independent control) to determine whether it mediates the observed lipid change. For the natural compounds, this column reads "No" without exception. For the pharmacological agents, the question does not arise in the same form, since the agent is defined by its target. Note 3. No study in this literature measured ANGPTL3–ANGPTL8 or ANGPTL4–ANGPTL8 complex formation, and no study measured LPL activity at the capillary endothelium of a peripheral tissue.

4.4. Benchmark: Human Genetic and Clinical Evidence for Pharmacological Angptl Inhibitors

By contrast, the pharmacological ANGPTL-inhibitor literature rests on a substantially more mature evidentiary foundation. Human loss-of-function genetic variants in ANGPTL3

causally link lifelong ANGPTL3 deficiency to a 34–41% reduction in coronary artery disease risk without an apparent adverse phenotype, providing target validation of a kind unavailable for any natural compound discussed here [5,6]. This genetic evidence validates ANGPTL3 as a molecular target rather than any individual agent, and is presented here separately from the efficacy data that follow. Evinacumab, a fully human monoclonal antibody against ANGPTL3, reduced triglycerides by approximately 76%, LDL-C by 23%, and HDL-C by 18% in initial studies in healthy individuals, with subsequent trials confirming lipid lowering in hypertriglyceridemic patients and in familial hypercholesterolemia; it is approved for homozygous familial hypercholesterolemia [4]. Vupanorsen, an antisense oligonucleotide targeting hepatic ANGPTL3 mRNA, produced triglyceride reductions of 33–63% across dose-ranging trials [4], but its development was discontinued after the phase 2b TRANSLATE-TIMI 70 trial: although the primary endpoint was met, the magnitude of non-HDL-C and triglyceride lowering was modest, liver enzyme elevations were more frequent at higher total monthly doses, and hepatic fat fraction increased in a dose-related manner [4]. Whether these hepatic findings reflect an on-target consequence of hepatic ANGPTL3 knockdown or an effect specific to the antisense modality is unresolved, and they cannot be extended automatically to antibody or small interfering RNA agents directed at the same target, still less to dietary compounds producing far smaller changes in ANGPTL3. Zodasiran, a small interfering RNA agent, lowered triglycerides by up to 63% and ANGPTL3 by up to 74% in a phase 2b trial and has since entered phase 3, and monoclonal antibodies directed against ANGPTL8 or the ANGPTL3-ANGPTL8 complex, including LY3475766, which reduced triglycerides by 70% after a single dose in a phase 1 trial, extend this pharmacological validation to additional axis nodes [8,9,39,40]. This body of human genetic, dose-ranging, and outcome-adjacent clinical trial evidence establishes a clear evidentiary ceiling against which the preclinical natural-compound literature must be judged: while mechanistically plausible and, in the case of cottonseed oil, supported by direct human ANGPTL measurements, no natural bioactive compound reviewed here has been evaluated in adequately powered, long-duration human trials with cardiovascular or even surrogate lipid endpoints comparable to those available for biologic ANGPTL inhibitors. These pharmacological ANGPTL3/4/8-directed agents are listed in Table 4 as an evidentiary benchmark against which the natural-compound literature is judged throughout this review.

Table 4. Pharmacological ANGPTL3/4/8-directed agents referenced as an evidentiary benchmark.

Agent	Modality	Target	Status	Key Efficacy Signal
Evinacumab	Fully human monoclonal antibody	ANGPTL3	Approved (homozygous FH)	TG ↓ ~76%; LDL-C ↓ ~23%; HDL-C ↓ ~18% (healthy individuals)
Vupanorsen	Antisense oligonucleotide	Hepatic ANGPTL3 mRNA	Phase 2 (discontinued)	TG ↓ 33–63% across doses; discontinued on modest efficacy with ↑ hepatic fat and ↑ ALT/AST
Zodasiran	Small interfering RNA	Hepatic ANGPTL3 mRNA	Phase 3	TG ↓ up to 63%; ANGPTL3 ↓ up to 74% (phase 2b)
REGN3776	Monoclonal antibody	ANGPTL8/ANGPTL3–8 complex	Preclinical	TG ↓ ~65% in humanized ANGPTL8 mice; dose-dependent TG ↓ in monkeys
LY3475766	Monoclonal antibody	ANGPTL3–8 complex	Phase 1 completed	TG ↓ 70%; remnant-C ↓ 86%; LDL-C ↓ 32%; HDL-C ↑ 27% (single dose)

5. Clinical Translation: Opportunities and Limitations

5.1. Pharmacokinetic and Bioavailability Constraints

The polymethoxyflavones nobiletin and tangeretin, despite the consistency of their in vitro effects on ANGPTL3 transcription and secretion [10,11], are known more broadly in the flavonoid pharmacology literature to exhibit limited and variable oral bioavailability and extensive glucuronidation; in rats, oral absorption of nobiletin was nearly 10-fold higher than that of tangeretin, and circulating glucuronide metabolites exceeded aglycone concentrations, indicating serum levels far below the micromolar concentrations required for ANGPTL3 suppression in hepatocyte culture, although comparable human pharmacokinetic data are lacking [41]. Achieving hepatic exposure sufficient to replicate the 20–40 μM effective concentrations reported in cell culture through dietary citrus intake alone is unlikely and would more plausibly require standardized extracts, bioavailability-enhancing formulations (e.g., nanoparticle or phospholipid complex delivery), or pharmacokinetically optimized analogs, none of which have yet been evaluated for ANGPTL3 endpoints in vivo.

5.2. Interspecies Dose Translatability

Effective doses in rodent and zebrafish models, whether expressed as dietary percentage (chitosan, quercetin), milligram-per-kilogram supplementation (ALA, royal jelly fatty acids), or extract concentration (raspberry polyphenols), do not translate directly to human dietary equivalents without allometric scaling and, ideally, human pharmacokinetic confirmation. The cottonseed oil trials [13–15,37] are notable precisely because they were conducted directly in humans at dietary-equivalent intakes, avoiding this translational uncertainty, and this may partly explain why cottonseed oil currently constitutes the most clinically credible natural-compound candidate in this review.

5.3. Target Selectivity and Safety Considerations

The pharmacological development experience with ANGPTL4 inhibition, whose severe phenotype derives principally from Angptl4-knockout mice on a high-saturated-fat diet and has not been reproduced in non-human primates treated with an inhibitory antibody or in humans carrying loss-of-function variants (Section 2.2) [4,34,35], illustrates that the safety of each node of the ANGPTL3/4/8 axis must be judged on species-appropriate evidence, and this consideration should inform interpretation of natural compounds that suppress ANGPTL4 (raspberry polyphenols, ALA) as opposed to those acting on ANGPTL3 (nobiletin, tangeretin) or ANGPTL8 (royal jelly sebacic acid). No natural-compound study reviewed here has assessed lymphatic or mesenteric safety endpoints, and this represents an important gap given the preclinical toxicity signal associated with pharmacological ANGPTL4 inhibition specifically. Selectivity is a parallel and unexamined concern for the transcriptional mechanisms proposed in Section 3: antagonism of LXRα would be expected to affect ABCA1, ABCG1, SREBP-1c, and CYP7A1-dependent processes, and reduction of HNF4α protein would affect the wider hepatocyte gene program, neither of which has been assessed for any natural compound reviewed here.

5.4. Positioning Within the Therapeutic Landscape

Within the broader landscape of lipid-lowering therapeutics, which includes statins, PCSK9 inhibitors (including the small interfering RNA agent inclisiran), ezetimibe, bempedoic acid, fibrates, and the emerging biologic ANGPTL3/4/8-directed agents [1], natural bioactive compounds acting on the ANGPTL axis are best positioned, on current evidence, as adjunctive or dietary-pattern-level interventions for mild-to-moderate atherogenic dyslipidemia or metabolic dysfunction-associated steatotic liver disease, rather than as substitutes

for guideline-directed pharmacotherapy in severe dyslipidemia such as homozygous familial hypercholesterolemia, for which biologic ANGPTL3 inhibitors have an established evidentiary and regulatory basis. This positioning parallels that of other natural products with cardiometabolic relevance, including berberine, red yeast rice, plant sterols, and marine omega-3 formulations [1], which occupy a complementary rather than replacement role alongside conventional pharmacotherapy.

5.5. Research Priorities

Advancing this field will require, at minimum: (i) human pharmacokinetic studies establishing whether achievable dietary or supplement-derived exposures to nobiletin, tangeretin, or sebacic acid reach concentrations sufficient for ANGPTL3/ANGPTL8 suppression; (ii) adequately powered human RCTs with direct ANGPTL3, ANGPTL4, and ANGPTL8 measurement as primary or key secondary endpoints, following the design template established by the cottonseed oil trials; (iii) mechanistic studies confirming or excluding ANGPTL dependence for compounds, such as quercetin, whose lipid-lowering activity may operate through parallel pathways; (iv) longer-duration safety monitoring, including hepatic fat and transaminases, which were measured in no natural-compound study reviewed here; (v) studies pairing tissue-resolved ANGPTL measurement with tissue-resolved LPL activity and lipid uptake, since the direction of an ANGPTL4 change is not interpretable on its own; and (vi) assessment of the wider consequences of reducing pleiotropic transcriptional regulators such as LXRα and HNF4α. Without these steps, the mechanistic promise documented in Section 3 cannot be responsibly translated into dietary or nutraceutical recommendations.

5.6. Oxidative Stress, Angptl8 Pleiotropy, and Exercise as Complementary Modulators

Beyond its direct regulatory role in triglyceride hydrolysis, the ANGPTL3/4/8 axis operates within a broader pathophysiological context in which oxidative stress and atherogenic dyslipidemia are mechanistically intertwined: triglyceride-rich lipoproteins and their remnants are preferentially susceptible to oxidative modification, and the resulting oxidized low-density lipoprotein (oxLDL) and small dense LDL particles are potent drivers of endothelial dysfunction, foam-cell formation, and vascular inflammation [42]. Because natural bioactive compounds that suppress ANGPTL3, ANGPTL4, or ANGPTL8 act primarily by lowering circulating triglyceride-rich lipoprotein burden rather than by direct antioxidant scavenging, their cardiovascular benefit may be partly mediated by a reduction in the substrate available for oxidative modification. This remains a proposed mechanism rather than an observed one: no study reviewed in Section 3 measured oxLDL, small dense LDL, or any other index of lipoprotein oxidative modification [42,43].

A further consideration that should temper enthusiasm for indiscriminate ANGPTL8 suppression is evidence that ANGPTL8 is not a purely pathogenic hepatokine. Beyond its role in stabilizing ANGPTL3 to inhibit LPL, ANGPTL8 also promotes triglyceride partitioning into white adipose tissue and has been associated with improved insulin sensitivity through Akt/GSK3β/FoxO1 signaling, suggesting that it may serve an adaptive, buffering function in postprandial lipid handling [44]. Natural compounds such as royal jelly-derived sebacic acid that act specifically by suppressing hepatic ANGPTL8 transcription through HNF4α (Section 3.3) should therefore be evaluated not only for their lipid-lowering efficacy but also for potential effects on adipose triglyceride storage and insulin sensitivity, an assessment that, to our knowledge, has not been undertaken in the existing literature [44].

Finally, the natural bioactive compounds reviewed here should be considered alongside exercise training, a non-pharmacological intervention with direct, human-validated effects on the ANGPTL axis that has received comparatively little attention in this context. In

the HERITAGE Family Study, twenty weeks of supervised endurance exercise training significantly reduced circulating ANGPTL3-ANGPTL8 complex levels, and this reduction correlated with increased LPL activity, decreased hepatic lipase activity, and favorable changes in triglycerides, apolipoprotein B, visceral fat, and fasting insulin [45]. This human evidence base is more direct than that available for any of the natural compounds discussed in Section 3, and it raises the possibility that combining ANGPTL-modulating natural compounds with structured exercise could produce additive or synergistic reductions in ANGPTL3/8 and ANGPTL4/8 complex activity; testing this combination directly is a further research priority beyond those outlined in Section 5.5.

6. Conclusions

The ANGPTL3/4/8 axis is a genetically and pharmacologically validated regulator of triglyceride-rich lipoprotein metabolism, and an expanding preclinical literature demonstrates that structurally diverse natural bioactive compounds, including citrus polymethoxyflavones, raspberry polyphenols, royal jelly fatty acids, dietary oils and fatty acids, chitosan, and flavonols, can engage this axis, predominantly by suppressing ANGPTL3 transcription through a mechanism provisionally attributed to LXRα but not yet confirmed at the receptor level, by suppressing ANGPTL8 transcription through HNF4α, or by modulating tissue-specific ANGPTL4 expression. For no compound has ANGPTL modulation been shown to mediate the lipid change observed. This evidence base, however, remains overwhelmingly preclinical, mechanistically heterogeneous, and, with the notable exception of cottonseed oil, unsupported by direct human ANGPTL measurement or adequately powered clinical trials. Set against the mature human genetic validation and clinical trial record supporting biologic ANGPTL3/4/8-directed pharmacotherapy, natural bioactive compounds currently occupy an early, hypothesis-generating tier of the evidence hierarchy. Realizing their translational potential as adjunctive nutraceutical strategies for dyslipidemia and cardiometabolic disease will depend on closing the gaps in bioavailability, dose translatability, and clinical trials identified in this review.

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Abbreviations

10H2DA	10-hydroxy-2-decenoic acid
10HDA	10-hydroxydecanoic acid
ALA	α-linolenic acid
AMPK	AMP-activated protein kinase
ANGPTL	angiopoietin-like protein
apoB	apolipoprotein B
ApoE	apolipoprotein E
ASCVD	atherosclerotic cardiovascular disease
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
CAD	coronary artery disease
CRP	C-reactive protein
CSO	cottonseed oil
DR1	direct repeat 1
EL	endothelial lipase
Elovl3	elongation of very long chain fatty acids protein 3
FFA	free fatty acid
FOS	fructo-oligosaccharide
GalNAc	N-acetylgalactosamine
GPIHBP1	glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
HDL-C	high-density lipoprotein cholesterol
HFD	high-fat diet
HNF-1α	hepatocyte nuclear factor 1 alpha
HNF4α	hepatocyte nuclear factor 4 alpha
HoFH	homozygous familial hypercholesterolemia
HOMA-IR	homeostatic model assessment of insulin resistance
IL-6	interleukin-6
LA	linoleic acid
LBD	ligand-binding domain
LDL-C	low-density lipoprotein cholesterol
LOF	loss of function
LPL	lipoprotein lipase
LXRα	liver X receptor alpha
mAb	monoclonal antibody
MDA	malondialdehyde
MTTP	microsomal triglyceride transfer protein
MW	molecular weight
NAFL(D)	nonalcoholic fatty liver (disease)
NF-κB	nuclear factor kappa B
NLRP3	NOD-like receptor family pyrin domain containing 3
Nrf2	nuclear factor erythroid 2-related factor 2
OO	olive oil
oxLDL	oxidized low-density lipoprotein
PCSK9	proprotein convertase subtilisin/kexin type 9
PMF	polymethoxylated flavone
PPAR	peroxisome proliferator-activated receptor
RCT	randomized controlled trial
RNAi	RNA interference
SA	sebacic acid
siRNA	small interfering RNA
SREBP	sterol regulatory element-binding protein
TC	total cholesterol
TG	triglyceride
TGRL	triglyceride-rich lipoprotein
TNF-α	tumor necrosis factor alpha
Ucp1	uncoupling protein 1
VLDL	very-low-density lipoprotein
WAT	white adipose tissue

References

1. Cui, D.; Yu, X.; Guan, Q.; Shen, Y.; Liao, J.; Liu, Y.; Su, Z. Cholesterol metabolism: Molecular mechanisms, biological functions, diseases, and therapeutic targets. *Mol. Biomed.* **2025**, *6*, 72. [CrossRef] [PubMed]
2. Dijk, W.; Kersten, S. Regulation of lipid metabolism by angiopoietin-like proteins. *Curr. Opin. Lipidol.* **2016**, *27*, 249–256. [CrossRef] [PubMed]
3. Zhang, R. The ANGPTL3-4-8 model, a molecular mechanism for triglyceride trafficking. *Open Biol.* **2016**, *6*, 150272. [CrossRef] [PubMed]
4. Sylvers-Davie, K.L.; Davies, B.S.J. Regulation of lipoprotein metabolism by ANGPTL3, ANGPTL4, and ANGPTL8. *Am. J. Physiol. Endocrinol. Metab.* **2021**, *321*, E493–E508. [CrossRef] [PubMed]
5. Kersten, S. Angiopoietin-like 3 in lipoprotein metabolism. *Nat. Rev. Endocrinol.* **2017**, *13*, 731–739. [CrossRef] [PubMed]
6. Chen, P.-Y.; Gao, W.-Y.; Liou, J.-W.; Lin, C.-Y.; Wu, M.-J.; Yen, J.-H. Angiopoietin-like protein 3 (ANGPTL3) modulates lipoprotein metabolism and dyslipidemia. *Int. J. Mol. Sci.* **2021**, *22*, 7310. [CrossRef] [PubMed]
7. Ruscica, M.; Zimetti, F.; Adorni, M.P.; Sirtori, C.R.; Lupo, M.G.; Ferri, N. Pharmacological aspects of ANGPTL3 and ANGPTL4 inhibitors: New therapeutic approaches for the treatment of atherogenic dyslipidemia. *Pharmacol. Res.* **2020**, *153*, 104653. [CrossRef] [PubMed]
8. Rosenson, R.S.; Gaudet, D.; Hegele, R.A.; Ballantyne, C.M.; Nicholls, S.J.; Lucas, K.J.; San Martin, J.; Zhou, R.; Muhsin, M.; Chang, T.; et al. Zodasiran, an RNAi therapeutic targeting ANGPTL3, for mixed hyperlipidemia. *N. Engl. J. Med.* **2024**, *391*, 913–925. [CrossRef] [PubMed]
9. Vahdat-Lasemi, F.; Farhoudi, L.; Hosseinikhah, S.M.; Santos, R.D.; Sahebkar, A. Angiopoietin-like protein inhibitors: Promising agents for the treatment of familial hypercholesterolemia and atherogenic dyslipidemia. *Atherosclerosis* **2025**, *405*, 119235. [CrossRef] [PubMed]
10. Lin, C.-Y.; Chen, P.-Y.; Hsu, H.-J.; Gao, W.-Y.; Wu, M.-J.; Yen, J.-H. The citrus flavonoid nobiletin downregulates angiopoietin-like protein 3 (ANGPTL3) expression and exhibits lipid-modulating effects in hepatic cells and adult zebrafish models. *Int. J. Mol. Sci.* **2022**, *23*, 12485. [CrossRef] [PubMed]
11. Chen, P.-Y.; Chao, T.-Y.; Hsu, H.-J.; Wang, C.-Y.; Lin, C.-Y.; Gao, W.-Y.; Wu, M.-J.; Yen, J.-H. The lipid-modulating effect of tangeretin on the inhibition of angiopoietin-like 3 (ANGPTL3) gene expression through regulation of LXRα activation in hepatic cells. *Int. J. Mol. Sci.* **2021**, *22*, 9853. [CrossRef] [PubMed]
12. Fotschki, B.; Juśkiewicz, J.; Jurgoński, A.; Sójka, M. Fructo-oligosaccharides and pectins enhance beneficial effects of raspberry polyphenols in rats with nonalcoholic fatty liver. *Nutrients* **2021**, *13*, 833. [CrossRef] [PubMed]
13. Polley, K.R.; Oswell, N.J.; Pegg, R.B.; Paton, C.M.; Cooper, J.A. A 5-day high-fat diet rich in cottonseed oil improves cholesterol profiles and triglycerides compared to olive oil in healthy men. *Nutr. Res.* **2018**, *60*, 43–53. [CrossRef] [PubMed]
14. Kaviani, S.; Polley, K.R.; Dowd, M.K.; Cooper, J.A.; Paton, C.M. Differential response of fasting and postprandial angiopoietin-like proteins 3, -4, and -8 to cottonseed oil versus olive oil. *J. Funct. Foods* **2021**, *87*, 104802. [CrossRef]
15. Prater, M.C.; Scheurell, A.R.; Paton, C.M.; Cooper, J.A. Eight weeks of daily cottonseed oil intake attenuates postprandial angiopoietin-like proteins 3 and 4 responses compared to olive oil in adults with hypercholesterolemia: A secondary analysis of a randomized clinical trial. *Nutr. Res.* **2024**, *123*, 88–100. [CrossRef] [PubMed]
16. Butler, A.A.; Graham, J.L.; Stanhope, K.L.; Wong, S.; King, S.; Bremer, A.A.; Krauss, R.M.; Hamilton, J.; Havel, P.J. Role of angiopoietin-like protein 3 in sugar-induced dyslipidemia in rhesus macaques: Suppression by fish oil or RNAi. *J. Lipid Res.* **2020**, *61*, 376–386. [CrossRef] [PubMed]
17. Nielsen, S.D.; Amer, B.; Blaabjerg, K.; Dalsgaard, T.K.; Jessen, R.; Petrat-Melin, B.; Rasmussen, M.K.; Poulsen, H.D.; Young, J.F. Whole milk increases intestinal ANGPTL4 expression and excretion of fatty acids through feces and urine. *J. Agric. Food Chem.* **2017**, *65*, 281–290. [CrossRef] [PubMed]
18. Inoue, Y.; Ienaga, M.; Kamiya, T.; Adachi, T.; Ohta, M.; Hara, H. Royal jelly fatty acids downregulate ANGPTL8 expression through the decrease in HNF4α protein in human hepatoma HepG2 cells. *Biosci. Biotechnol. Biochem.* **2022**, *86*, 747–754. [CrossRef] [PubMed]
19. Liu, S.-H.; Chiu, C.-Y.; Shi, C.-M.; Chiang, M.-T. Functional comparison of high and low molecular weight chitosan on lipid metabolism and signals in high-fat diet-fed rats. *Mar. Drugs* **2018**, *16*, 251. [CrossRef] [PubMed]
20. Kuipers, E.N.; van Dam, A.D.; Held, N.M.; Mol, I.M.; Houtkooper, R.H.; Rensen, P.C.N.; Boon, M.R. Quercetin lowers plasma triglycerides accompanied by white adipose tissue browning in diet-induced obese mice. *Int. J. Mol. Sci.* **2018**, *19*, 1786. [CrossRef] [PubMed]
21. Shanmugam, G. Polyphenols: Potent protectors against chronic diseases. *Nat. Prod. Res.* **2024**, *39*, 3941–3943. [CrossRef] [PubMed]

22. Jomova, K.; Alomar, S.Y.; Valko, R.; Liska, J.; Nepovimova, E.; Kuca, K.; Valko, M. Flavonoids and their role in oxidative stress, inflammation, and human diseases. *Chem. Biol. Interact.* **2025**, *413*, 111489. [CrossRef] [PubMed]
23. Rudrapal, M.; Khairnar, S.J.; Khan, J.; Dukhyil, A.B.; Ansari, M.A.; Alomary, M.N.; Alshabrmi, F.M.; Palai, S.; Deb, P.K.; Devi, R. Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism(s) of action. *Front. Pharmacol.* **2022**, *13*, 806470. [CrossRef] [PubMed]
24. Nakadate, K.; Ito, N.; Kawakami, K.; Yamazaki, N. Anti-inflammatory actions of plant-derived compounds and prevention of chronic diseases: From molecular mechanisms to applications. *Int. J. Mol. Sci.* **2025**, *26*, 5206. [CrossRef] [PubMed]
25. Dama, A.; Shpati, K.; Daliu, P.; Dumur, S.; Gorica, E.; Santini, A. Targeting metabolic diseases: The role of nutraceuticals in modulating oxidative stress and inflammation. *Nutrients* **2024**, *16*, 507. [CrossRef] [PubMed]
26. Barros, J.; Abraão, A.; Gouvinhas, I.; Granato, D.; Barros, A.N. Advances in leaf plant bioactive compounds: Modulation of chronic inflammation related to obesity. *Int. J. Mol. Sci.* **2025**, *26*, 3358. [CrossRef] [PubMed]
27. Muscolo, A.; Mariateresa, O.; Giulio, T.; Mariateresa, R. Oxidative stress: The role of antioxidant phytochemicals in the prevention and treatment of diseases. *Int. J. Mol. Sci.* **2024**, *25*, 3264. [CrossRef] [PubMed]
28. Bolgova, O.; Shypilova, I.; Mavrych, V. Natural strategies to optimize estrogen levels in aging women: Mini review. *Front. Aging* **2025**, *6*, 1706117. [CrossRef] [PubMed]
29. Shypilova, I.; Bolgova, O.; Mavrych, V. Integrative natural approaches for age-related testosterone decline: A synergistic framework combining exercise, nutrition, and bioactive compounds. *Cureus* **2026**, *18*, e101276. [CrossRef] [PubMed]
30. Mavrych, V.; Shypilova, I.; Bolgova, O. Therapeutic peptides in gerontology: Mechanisms and applications for healthy aging. *Front. Aging* **2026**, *7*, 1790247. [CrossRef] [PubMed]
31. Musunuru, K.; Pirruccello, J.P.; Do, R.; Peloso, G.M.; Guiducci, C.; Sougnez, C.; Garimella, K.V.; Fisher, S.; Abreu, J.; Barry, A.J.; et al. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. *N. Engl. J. Med.* **2010**, *363*, 2220–2227. [CrossRef] [PubMed]
32. Dewey, F.E.; Gusarova, V.; Dunbar, R.L.; O'Dushlaine, C.; Schurmann, C.; Gottesman, O.; McCarthy, S.; Van Hout, C.V.; Bruse, S.; Dansky, H.M.; et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N. Engl. J. Med.* **2017**, *377*, 211–221. [CrossRef] [PubMed]
33. Stitziel, N.O.; Khera, A.V.; Wang, X.; Bierhals, A.J.; Vourakis, A.C.; Sperry, A.E.; Natarajan, P.; Klarin, D.; Emdin, C.A.; Zekavat, S.M.; et al. ANGPTL3 deficiency and protection against coronary artery disease. *J. Am. Coll. Cardiol.* **2017**, *69*, 2054–2063. [CrossRef] [PubMed]
34. Cummings, B.B.; Bouchard, P.R.; Milton, M.N.; Moesta, P.F.; Ramanan, V.; Trauger, J.; Maratos-Flier, E.; Voznesensky, A.; Splawski, I.; Nimonkar, A.; et al. An ANGPTL4 inhibitory antibody safely improves lipid profiles in non-human primates. *eBioMedicine* **2025**, *117*, 105748. [CrossRef] [PubMed]
35. Gusarova, V.; O'Dushlaine, C.; Teslovich, T.M.; Benotti, P.N.; Mirshahi, T.; Gottesman, O.; Van Hout, C.V.; Murray, M.F.; Mahajan, A.; Nielsen, J.B.; et al. Genetic inactivation of ANGPTL4 improves glucose homeostasis and is associated with reduced risk of diabetes. *Nat. Commun.* **2018**, *9*, 2252. [CrossRef] [PubMed]
36. Hart, T.L.; Petersen, K.S.; Kris-Etherton, P.M. The effect of cottonseed oil on lipids/lipoproteins: A systematic review and plasma cholesterol predictive equations estimations. *Nutr. Rev.* **2024**, *82*, 1079–1086. [CrossRef] [PubMed]
37. Prater, M.C.; Scheurell, A.R.; Paton, C.M.; Cooper, J.A. Blood lipid responses to diets enriched with cottonseed oil compared with olive oil in adults with high cholesterol in a randomized trial. *J. Nutr.* **2022**, *152*, 2060–2071. [CrossRef] [PubMed]
38. Rajna, A.; Gibling, H.; Sarr, O.; Matravadia, S.; Holloway, G.P.; Mutch, D.M. Alpha-linolenic acid and linoleic acid differentially regulate the skeletal muscle secretome of obese Zucker rats. *Physiol. Genom.* **2018**, *50*, 580–589. [CrossRef] [PubMed]
39. Gaudet, D.; Gonciarz, M.; Shen, X.; Leohr, J.K.; Beyer, T.P.; Day, J.W.; Mullins, G.R.; Zhen, E.Y.; Hartley, M.; Larouche, M.; et al. Targeting the angiopoietin-like protein 3/8 complex with a monoclonal antibody in patients with mixed hyperlipidemia: A phase 1 trial. *Nat. Med.* **2025**, *31*, 2632–2639. [CrossRef] [PubMed]
40. Bitencourt, I.C.; Zimerman, A.; Marston, N.A. The angiopoietin-like protein (ANGPTL) axis in dyslipidemia: Mechanisms, cardiovascular risk, and emerging therapies. *Curr. Atheroscler. Rep.* **2026**, *28*, 70. [CrossRef] [PubMed]
41. Manthey, J.A.; Cesar, T.B.; Jackson, E.; Mertens-Talcott, S. Pharmacokinetic study of nobiletin and tangeretin in rat serum by high-performance liquid chromatography-electrospray ionization-mass spectrometry. *J. Agric. Food Chem.* **2011**, *59*, 145–151. [CrossRef] [PubMed]
42. Vekic, J.; Stromsnes, K.; Mazzalai, S.; Zeljkovic, A.; Rizzo, M.; Gambini, J. Oxidative stress, atherogenic dyslipidemia, and cardiovascular risk. *Biomedicines* **2023**, *11*, 2897. [CrossRef] [PubMed]
43. Kulkarni, A.; Kulkarni, C.C.; Pradeep, S.R.; Poyya, J.; Kudva, A.K.; Radhakrishnan, V.; Khandagale, A.S. Role of anti-inflammatory and antioxidant properties of natural products in curing cardiovascular diseases. *Curr. Issues Mol. Biol.* **2025**, *47*, 955. [CrossRef] [PubMed]

44. Guo, C.; Wang, C.; Deng, X.; He, J.; Yang, L.; Yuan, G. ANGPTL8 in metabolic homeostasis: More friend than foe? *Open Biol.* **2021**, *11*, 210106. [CrossRef] [PubMed]
45. Hoffmann, W.G.; Chen, Y.Q.; Schwartz, C.S.; Barber, J.L.; Dev, P.K.; Reasons, R.J.; Miranda Maravi, J.S.; Armstrong, B.; Gerszten, R.E.; Silbernagel, G.; et al. Effects of exercise training on ANGPTL3/8 and ANGPTL4/8 and their associations with cardiometabolic traits. *J. Lipid Res.* **2024**, *65*, 100495. [CrossRef] [PubMed]

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