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REVIEW ARTICLE

Analysis of Low Molecular Weight Substances and Related Processes Influencing Cellular Cholesterol Efflux

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Abstract

Cholesterol efflux is the key process protecting the vascular system from the development of atherosclerotic lesions. Various extracellular and intracellular events affect the ability of the cell to efflux excess cholesterol. To explore the possible pathways and processes that promote or inhibit cholesterol efflux, we applied a combined cheminformatic and bioinformatic approach. We performed a comprehensive analysis of published data on the various substances influencing cholesterol efflux and found 153 low molecular weight substances that are included in the Chemical Entities of Biological Interest (ChEBI) database. Pathway enrichment was performed for substances identified within the Reactome database, and 45 substances were selected in 93 significant pathways. The most common pathways included the energy-dependent processes related to active cholesterol transport from the cell, lipoprotein metabolism and lipid transport, and signaling pathways. The activators and inhibitors of cholesterol efflux were non-uniformly distributed among the different pathways: the substances influencing 'biological oxidations' activate cholesterol efflux and the substances influencing 'Signaling by GPCR and PTK6' inhibit efflux. This analysis may be used in the search and design of efflux effectors for therapies targeting structural and functional high-density lipoprotein deficiency.

Key Points

We performed a comprehensive analysis of the various substances influencing cholesterol efflux, with pathway enrichment using the Reactome database.

The activators and inhibitors of cholesterol efflux are non-uniformly distributed among different pathways.

The substances influencing biological oxidation activate cholesterol efflux, and the substances influencing signaling by G protein-coupled receptors (GPCR) and non-receptor tyrosine kinase (PTK6) inhibit efflux.

1 Reverse Cholesterol Transport

High-density lipoprotein (HDL) heterogeneity influences its atheroprotective effect via reverse cholesterol transport from macrophage to the liver [1]. Cholesterol efflux from a macrophage to the extracellular cholesterol acceptor is the first, and rate-limiting, step of reverse cholesterol transport [2, 3]. Four mechanisms of cholesterol efflux, namely aqueous diffusion, facilitated diffusion mediated by the scavenger receptor class B member 1 (SR-B1) receptor, and active unidirectional efflux mediated by the ATP binding cassette subfamily A member 1 (ABCA1) and the ATP binding cassette subfamily G member 1 (ABCG1) transporters are known [4]. ATP hydrolysis with concomitant conformational transition is required for cholesterol efflux by ABCA1 and ABCG1 transporters. The SR-B1 mediates cholesterol efflux by facilitated diffusion via hydrophobic tunnel within the molecule. Various HDL fractions and lipid-free apolipoprotein A1 (apoA-1) are able to accept cell-derived cholesterol with a different efficiency [2]. Cholesterol transport between intracellular compartments proceeds by both energy-dependent and energy-independent processes [5]. The energy-dependent vesicular traffic partly contributes to cholesterol flux between endoplasmic reticulum, plasma membrane (PM) and endocytic vesicles. The membrane contact sites and lipid transfer proteins are involved in non-vesicular lipid traffic [6–11]. Importantly, the PM cholesterol is the cholesterol that participates in the efflux to the extracellular acceptors [12].

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Cholesterol efflux from the macrophage is clinically significant for two reasons. First, there is a significant relationship between the cholesterol efflux capacity (CEC) of apolipoprotein B (apoB)-depleted plasma and the manifestations of various cardiovascular events. The predictive significance of CEC for cardiovascular risk is stronger than for HDL cholesterol level [13–16]. The second reason is the positive effect of efflux stimulation on the regression of atherosclerotic plaques [15, 17, 18].

The molecular events in cellular cholesterol efflux, along with the contribution of various pathways, have been extensively studied; however, there is no systematic evaluation of the influence of various low molecular weight substances on cholesterol efflux as a process directed by both donor and acceptor participants. A combined cheminformatic and bioinformatic approach has been applied in the present review to classify and compare the known efflux effectors. Our work may be applicable in the targeted therapy of structural and functional HDL deficiency.

2 Effectors of Cholesterol Efflux

The PubMed database was initially searched using the term 'cholesterol efflux', and papers involving the use of low molecular weight substances were selected. This analysis of published data on the influence of low molecular weight substances on cholesterol efflux with various donors and acceptors revealed 191 substances with activating and inhibiting effects (Table 1). These substances were grouped into the following classes by means of small-molecule high-throughput screening (Fig. 1): (1) inhibitors and activators of SR-B1 receptors or ABC transporters, including sulfonylureas (inhibitors of ATP-sensitive K+ channels); (2) cyclic nucleotides, nucleotide triphosphates, ligands of nucleotide-dependent protein kinases; (3) nuclear receptor ligands and their precursors; (4) cytokines and their receptors; (5) hormones, hormone receptor ligands (excluding ligands of nuclear receptors), hormone metabolism and growth factors; (6) lipid metabolism—intracellular and extracellular; (7) fatty acids and lipid membrane-disturbing agents; (8) protein kinase B, mammalian target of rapamycin, phosphatidylinositol-phospholipase C; (9) ceramide signaling; (10) mitogen-activated protein kinase and non-receptor tyrosine kinase signaling; (11) ion channels and Ca2+ regulation; (12) protein synthesis and degradation; (13) structural and trafficking proteins and their ligands; (14) DNA-dependent processes; (15) other factors; (16) vitamins, coenzymes and metabolites; and (17) extracts, components of plants, and other natural sources. Overall, 153 substances were present in the Chemical Entities of Biological Interest (ChEBI) database [220].

The subsequent Reactome database search [221] identified 67 substances, and 9 substances were excluded due to dual activating and inhibiting properties. Pathway enrichment was then performed for the remaining 58 substances using the standard Reactome tools with a 'small molecules (chebi)' key. The significant ($p < 0.05$) 93 pathways were selected, including 45 from 58 substances. The number of significant pathways was reduced to 31 by the replacement of pathways of very low level with higher-level (parent) pathways (Table 2). These pathways included the Neuronal System (R-HSA-112316); transcriptional regulation of white adipocyte differentiation (R-HSA-381340); the citric acid (TCA) cycle and respiratory electron transport (R-HSA-1428517); integration of energy metabolism (R-HSA-163685); metabolism of vitamins and cofactors (R-HSA-196854); biological oxidations (R-HSA-211859); fatty acid metabolism (R-HSA-8978868); regulation of lipid metabolism by peroxisome proliferator-activated receptor-α (PPARα; R-HSA-400206); metabolism of steroids (R-HSA-8957322); metabolism of amino acids and derivatives (R-HSA-71291); cell junction organization (R-HSA-446728); signaling by nerve growth factor (R-HSA-166520); signaling by Wnt (R-HSA-195721); visual phototransduction (R-HSA-2187338); signaling by GPCR (R-HSA-372790); signaling by retinoic acid (R-HSA-5362517); death receptor signaling (R-HSA-73887); signaling by PTK6 (R-HSA-8848021); disorders of transmembrane transporters (R-HSA-5619115); diseases of signal transduction (R-HSA-5663202); metabolic disorders of biological oxidation enzymes (R-HSA-5579029); diseases of carbohydrate metabolism (R-HSA-5663084); immune system (R-HSA-168256); plasma lipoprotein assembly, remodeling, and clearance (R-HSA-174824); transport of bile salts and organic acids, metal ions, and amine compounds (R-HSA-425366); transport of vitamins, nucleosides, and related molecules (R-HSA-425397); metabolism of proteins (R-HSA-392499); circadian clock (R-HSA-400253); vesicle-mediated transport (R-HSA-5653656); RNA polymerase II transcription (R-HSA-73857); and digestion and absorption (R-HSA-8963743). Importantly, the energy-dependent processes (R-HSA-1428517, R-HSA-163685, R-HSA-211859, R-HSA-5619115, R-HSA-5579029), lipoprotein metabolism and lipid transport (R-HSA-400206, R-HSA-8957322, R-HSA-174824, R-HSA-5653656) and signaling pathways (R-HSA-166520, R-HSA-195721, R-HSA-372790, R-HSA-5362517, R-HSA-73887, R-HSA-8848021, R-HSA-5663202) are included (Table 2).

Table 1 Effect of some substances, drugs and natural extracts on cholesterol efflux in various cells for different cholesterol acceptors

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Inhibitors and activators of SR-B1 receptor or ABC transporters including sulfonylureas (inhibitors of ATP-sensitive K + channels)				
Stimulation				
Diphenoquinone	Supposedly an oxidized metabolite of probucol; inhibits calpain-mediated degradation of ABCA1	THP-1, HEK293 expressing ABCA1	ApoA-I	[19]
Glimepiride[b]	A sulfonylurea antidiabetic drug, inhibitor of ATP-sensitive K + channels	RAW 264.7	HDL	[20]
Glyburide[b] (glibenclamide)	A sulfonylurea antidiabetic drug; a general inhibitor of ABC transporters, including ABCA1	RAW 264.7	HDL	[20]
IMB2026791	An xanthone compound that enhances binding of apoA-I to ABCA1	CHO, CHO expressing ABCA1, THP-1 cells	ApoA-I, HDL (CHO expressing ABCA1, THP-1 cells)	[21]
Spiroquinone	Supposedly an oxidized metabolite of probucol; inhibits calpain-mediated degradation of ABCA1	THP-1, HEK293 expressing ABCA1	ApoA-I	[19]
Inhibition				
BLT-1 - BLT-5	Inhibitors of SR-B1; increases binding affinity of SR-B1 for HDL	ldlA-7 cells stably transfected to express SR-B1	HDL	[22]
BLT-1, BLT-4	Inhibitors of SR-B1; increases binding affinity of SR-B1 for HDL	RAW 264.7, 3T3 L-1-derived adipocytes	ApoA-I	[23, 24]
Compound 1 (methyl 3α-acetoxy-7α,12α-di[(phenylaminocarbonyl) amino]-5β-cholan-24-oate)	A novel inhibitor of ABCA1	RAW 264.7	ApoA-I, taurocholate, peptide 18A (i.e. 2F)	[25]
Compound 2 (*N*-[2-((4-nitrophenylaminocarbonyl)amino)ethyl]-*N*,*N*-di[2-((4-methylphenylsulfonyl) amino)ethyl]amine)	A novel inhibitor of ABCA1	RAW 264.7	ApoA-I	[25]
Glimepiride[b]	A sulfonylurea antidiabetic drug, inhibitor of ATP-sensitive K + channels	THP-1, HEK293 expressing ABCA1	ApoA-I	[20]
Glyburide[b] (glibenclamide)	A sulfonylurea antidiabetic drug; a general inhibitor of ABC transporters, including ABCA1	J774, RAW 264.7, THP-1, fibroblasts, SMC, HEK293 expressing ABCA1, 3T3 L-1-derived adipocytes	ApoA-I	[20, 23, 26, 27]
		BHK-21, BHK-21 expressing SR-B1	HDL	[20]
		J774	HDL3	[28]
Wheat germ agglutinin	A lectin; inhibits generation of microparticle by ABCA1	RAW 264.7	No acceptor	[25]
Probucol	An inhibitor of ABCA1-mediated lipid efflux, lipid-lowering drug, an antioxidant, stimulates cellular lipids synthesis	J774, MPM	ApoA-I, ApoA-II (MPM), ApoE (MPM)	[29–31]
		Astrocytes	ApoA-I, HDL, ApoE, conditioned medium	[32]
		THP-1, WI-38 human fibroblast cells, MAC-T	ApoA-I	[19, 33, 34]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
PSC833	Inhibits ABCA1; a non-immunosuppressive cyclosporine not inhibiting calcineurin; an inhibitor of ABCB1 and ABCB4	ABCA1-expressing BHK cells, THP-1	ApoA-I	[35]
Cyclic nucleotides, nucleotide triphosphates, ligands of nucleotide-dependent protein kinases				
Stimulation				
8-Br-cAMP	cAMP analog	RAW 264.7	ApoA-I, ApoE2, ApoE3, ApoE4, HDL	[36]
		J774, astrocytes	ApoA-I, HDL (astrocytes)	[23, 37]
A-769662	Activator of AMPK	THP-1	ApoA-I	[38]
ATP (up to 0.1–1 μM; inhibition over 1–10 μM)	Nucleoside triphosphate	RAW 264.7, ABCA1-expressing BHK cells	ApoA-I	[39]
ATP, 1 mM	Nucleoside triphosphate	Primary mouse type II pneumocytes	No acceptor	[40]
AICAR (5-aminoimidazole-4-carboxyamide ribonucleoside)	An activator of AMPK	J774	HDL	[41]
cpt-cAMP (8-(4-chlorophenylthio)-cAMP)	cAMP analog	MPM, J774, L-cell	ApoA-I, HDL3 (J774)	[28–30]
st-Ht31	PKA-anchoring inhibitor	ABCA1-expressing BHK cells, RAW 264.7	No acceptor; also ApoA-I in a separate experiment	[42]
Inhibition				
Apyrase	ATP hydrolysis to AMP	RAW 264.7 and ABCA1-expressing BHK cells	ApoA-I	[39]
MDL-12330A	An inhibitor of adenylate cyclase	RAW 264.7	ApoA-I	[43]
PKI	A PKA inhibitor	ABCA1-expressing BHK cells	ApoA-I	[44]
Oligomycin	An inhibitor of ATP synthase; inhibits mitochondrial respiration	THP-1	ApoA-I	[45]
Sodium orthovanadate	A specific inhibitor of P-type ATPases and protein phosphotyrosine phosphatases	Fibroblasts, SMC	ApoA-I	[26]
Nuclear receptor ligands and their precursors				
Stimulation				
9-cis-retinoic acid	A retinoid that activates RXRs and RARs	Astrocytes	ApoA-I, HDL	[46]
13-cis-retinoic acid	A retinoid that is neither an RAR nor an RXR agonist	Astrocytes	ApoA-I, HDL	[46]
13-hydroxy linoleic acid	Natural PPAR agonist	RAW 264.7	ApoA-I	[47]
22(R)-hydroxycholesterol	An oxysterol, natural LXR activator	hPBMC, mBMDM, RAW 264.7, THP-1	ApoA-I, HDL (THP-1)	[48–51]
22(R)-hydroxycholesterol with 9-cis-retinoic acid	LXR/RXR agonist	J774, MPM, astrocytes, primary mouse type II pneumocytes	ApoA-I, HDL (astrocytes, CaCo-2), no acceptor (CaCo-2)	[32, 40, 52–54]
24(S),25-epoxycholesterol	An oxysterol, natural LXR activator	mBMDM, hPBMC	ApoA-I	[48]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
9-cis-β-carotene	A precursor for 9-cis-retinoic acid that stimulates cholesterol efflux	RAW 264.7, MPM	HDL	[55]
Acetyl-podocarpic dimer	LXR agonist	hPBMC, THP-1, primary human fibroblasts	ApoA-I	[51]
All-trans β-carotene	Vitamin A precursor	RAW 264.7	HDL	[55]
All-trans retinoic acid (tretinoin)	A retinoid that activates RARs	Astrocytes	ApoA-I, HDL	[46]
Baicalin	PPARγ agonist	THP-1	HDL2, HDL3	[56]
Bezafibrate	A lipid-lowering fibrate drug, an agonist of PPARα	THP-1	apoB-depleted plasma	[57]
E17110	A novel benzofuran-2-carboxylate derivative with potential LXRβ agonist activity	RAW 264.7	ApoA-I, HDL	[58]
Ethyl 2,4,6-trihydroxybenzoate	An LXR agonist isolated from Celtis biondii	THP-1	HDL	[59]
Fenofibric acid	A fibrate; used for the treatment of dyslipidemia, a PPARα agonist	hPBMC	HDL	[60]
GW1929	PPARγ agonist	THP-1	HDL3, ApoA-I	[61]
GW3965	LXR agonist	MPM, RAW 264.7, THP-1, Huh7.5 (hepatoma cells), 3T3 L-1-derived adipocytes, blastic plasmacytoid dendritic cell neoplasm cell line CAL-1 (a myeloid leukemia cell line)	ApoA-I, HDL2 (THP-1, CAL-1), HDL3 (THP-1)	[23, 62–66]
GW4064	FXR agonist	THP-1	No acceptor	[67]
Isosylibin A	A partial PPARγ agonist	THP-1	ApoA-I	[68]
K-877	Selective PPARα modulator	hPBMC	HDL	[60]
Methoprene	Synthetic selective RXR agonist	Astrocytes	ApoA-I, HDL	[46]
N-Acylthiadiazoline compound 2 (racemate or R enantiomer)	LXRβ agonist	MPM	ApoA-I	[64]
Pioglitazone[b]	PPAR agonist	THP-1, RAW 264.7	ApoA-I, HDL, HDL2 (THP-1), HDL3 (THP-1), human plasma (THP-1)	[68–71]
Rosiglitazone	Synthetic PPAR agonist	hPBMC, MPM, THP-1	ApoA-I, HDL (THP-1), HDL2 (THP-1), HDL3 (THP-1)	[62, 72–74]
		RAW 264.7	HDL	[75]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
TO-1317 (TO-901317)	LXR agonist	J774, MPM, RAW 264.7, THP-1, CaCo-2, MAC-T (ApoA-I)	ApoA-I, HDL, HDL3 (MPM), no acceptor (THP-1), taurocholate-phosphatidylcholine micelles (CaCo-2)	[34, 54, 59, 76–81]
		Blastic plasmacytoid dendritic cell neoplasm cell line CAL-1 (a myeloid leukemia cell line)	ApoA-I, HDL2	[66]
		HepG2, human foreskin fibroblasts	ApoA-I	[82, 83]
Telmisartan	Angiotensin II receptor antagonist; also activates PPARγ	THP-1	ApoA-I, HDL2, HDL3	[70]
Tributyltin chloride	An organotin compound; an RXR activator	RAW 264.7	ApoA-I	[76]
Wy14643	PPARα activator	hPBMC	ApoA-I	[72]
Inhibition				
15d-PGJ2 (15-Deoxy-delta(12,14)-prostaglandin J(2))	PPARγ ligand	MPM	ApoA-I	[84]
Pioglitazone[b]	PPAR agonist	MPM	ApoA-I	[84]
Troglitazone	PPARγ and, to a lesser extent, PPARα agonist	MPM	ApoA-I	[84]
TTNPB (4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid)	Synthetic selective RAR agonist	Astrocytes	ApoA-I, HDL	[46]
Cytokines and their receptors				
Stimulation				
Apelin-13	An adipocytokine, a ligand for the cognate G-protein coupled receptor APJ	THP-1	ApoA-I	[85]
CXCL5	A chemokine that signals through the CXCR2 receptor	MPM	ApoA-I	[86]
IL-8-neutralizing antibody	IL-8 is a proinflammatory chemokine that induces chemotaxis and phagocytosis	THP-1	ApoA-I	[87]
IL-10	An anti-inflammatory cytokine	THP-1	ApoA-I, HDL2, serum (FBS)	[88]
IL-12 with IL-18	IL-12 and IL-18 synergize for the production of IFNγ	THP-1	ApoA-I	[89]
IL-27	An anti-inflammatory cytokine	THP-1	ApoA-I	[90]
TGFβ	An anti-inflammatory cytokine	MPM from WT or apoE KO mice	ApoA-I, HDL	[91]
TNFα[b]	Proinflammatory cytokine	MPM	ApoA-I	[92]
Inhibition				
CCL2	Pro-atherosclerotic chemokine	HCAEC, HUVEC	ApoA-I (HCAEC), HDL	[93]
IFNβ	Promotes atherogenesis in mice	mBMDM	ApoA-I	[94]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
IL-1β	Pro-inflammatory cytokine	HepG2, primary mouse hepatocytes	ApoA-I	[95]
IL-6	Pro-inflammatory cytokine	THP-1	ApoA-I	[96]
INFγ	Pro-inflammatory cytokine, has a variety of proatherogenic effects	MPM, THP-1	ApoA-I	[91, 97–99]
TNFα[b]	Pro-inflammatory cytokine	THP-1, HepG2, mouse primary hepatocytes, podocytes (kidney cells)	ApoA-I	[95, 96, 100]
TNF-like protein 1A (TL1A; TNFSF15)	Binds to DR3; highly expressed in atherosclerotic plaques	THP-1, hPBMC	ApoA-I	[99]
Visfatin (pre-B cell colony-enhancing factor 1)	A nicotinamide phosphoribosyltransferase	RAW 264.7	ApoA-I, HDL	[101]
Hormones, hormone receptor ligands (excluding ligands of nuclear receptors), hormone metabolism and growth factors				
Stimulation				
17β-estradiol	A steroid sex hormone	VSMC, MAC-T	ApoA-I, HDL (VSMC)	[34, 102]
Angiotensin-(1–7)	Produced by ACE2; ACE2-deficient mice have an increased risk of heart failure	THP-1, RAW 264.7	ApoA-I or HDL (THP-1)	[43, 103]
Exendin-4	A GLP-1 mimetic affecting insulin regulation	3T3-L1 adipocytes	No acceptor	[104]
FGF-21	Mitogenic and cell survival activities	THP-1	ApoA-I, HDL	[105]
Ghrelin	An endocrine peptide mainly identified in stomach epithelium; stimulates food intake in humans	THP-1	ND	[106]
GDP-15	A 12-kDa secreted protein, also named macrophage inhibitory cytokine-1	THP-1	No acceptor	[107]
Hydrocortisone (i.e. cortisol)	A steroid hormone, stimulates gluconeogenesis, suppresses the immune system	MAC-T	ApoA-I	[34]
IGF-1	Regulates metabolism, growth, and cell differentiation and survival	INS-1 cells originated from a rat insulinoma cell line	ND	[108]
Insulin[b)]	A peptide hormone, regulates glucose metabolism	MAC-T	ApoA-I	[34]
Progesterone	A steroid sex hormone	MAC-T	ApoA-I	[34]
Prolactin	A peptide hormone; initiates milk production	MAC-T	ApoA-I	[34]
Vildagliptin	An antidiabetic drug, an inhibitor of DPP-4, thus prolonging the half-life of GLP-1	3T3-L1 adipocytes	No acceptor	[104, 109]
Inhibition				
Adiponectin (Acrp30)	An adipokine secreted by adipocytes that functions as an insulin sensitizer	hPBMC	ApoA-I	[110]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Angiotensin-II	A peptide produced by the enzyme ACE; ACE inhibitors are used for the treatment of CVDs	THP-1	ApoA-I or HDL	[103]
CRH	A peptide that links psychological stress to pathophysiologic responses	MPM	ApoA-I	[111]
Dexamethasone	A corticosteroid, agonist of GR	THP-1	ApoA-I	[112]
EGF	Activates MAP kinases ERK1/2	RAW 264.7	ApoA-I	[113]
Hydrocortisone	A corticosteroid, agonist of GR	THP-1	Human serum	[114]
Insulin[b]	A peptide hormone, regulates glucose metabolism	hPBMC, HepG2, HEK293 expressing ABCA1	ApoA-I	[110, 115]
Raloxifene	A benzothiophene derivative that is used for the treatment of osteoporosis in postmenopausal women; a selective ER modulator: stimulates ER in bone and inhibits ER in the uterus and breast	THP-1, MPM	ApoA-I, HDL	[116]
Tamoxifen	A medication for treating breast cancer; a prodrug that is metabolized in the liver into an ER antagonist	THP-1, MPM	ApoA-I, HDL	[116]
Toremifene	A selective ER modulator; a medication for treating breast cancer	THP-1, MPM	ApoA-I, HDL	[116]
Lipid metabolism—intracellular and extracellular				
Stimulation				
Ibrolipim	An LPL activator	THP-1	ApoA-I, HDL	[117]
MCC-147	An inhibitor of ACAT	MPM	ApoA-I	[118]
Myriocin	An inhibitor of SPTLC1	Primary human fibroblasts, mBMDM	ApoA-I	[119]
NTE-122 (trans-1,4-bis [[1 -cycIohexyI-3-(4-dimethyIamino phenyl)ureido]methyl]cyclohexane)	An inhibitor of ACAT	THP-1	HDL	[120]
PLTP[b]	Transfers phospholipids between lipoproteins, remodels HDL	J774, BHK expressing ABCA1	HDL, trypsinized HDL	[121]
		BHK expressing ABCA1	No acceptor, LDL, phospholipid vesicles	[121]
Pitavastatin[b]	Relatively lipophilic statin; type II statin[c]	Fu5AH	ApoA-I	[122]
Simvastatin[b]	Relatively lipophilic statin; type I statin[c]	THP-1	ApoB-depleted plasma	[57]
Inhibition				
LPL	A secreted enzyme facilitating the hydrolysis of triglycerides in chylomicrons	THP-1	ApoA-I	[123]
PLTP[b]	Transfers phospholipids between lipoproteins, remodels HDL	BHK expressing ABCA1	ApoA-I	[121]
PCSK9	A subtilisin family-serine protease that degrades LDL receptor in liver	MPM	ApoA-I	[53]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Simvastatin[b] (0.01 μM)	Relatively lipophilic statin; type I statin[c]	J774	ApoA-I	[124]
		THP-1, hPBMC	HDL	[125]
Atorvastatin (10 μM)	Relatively lipophilic statin; type II statin[c]	J774, RAW 264.7	ApoA-I	[124, 126]
		THP-1, hPBMC	HDL, ApoA-I (THP-1)	[125, 127]
Rosuvastatin (10 μM)	Relatively hydrophilic statin; type II statin[c]	J774	ApoA-I	[124]
Pitavastatin[b)] (0.1 or 1 μM for J774, RAW—depends on the paper)	Relatively lipophilic statin; type II statin[c]	J774, MPM, RAW 264.7	ApoA-I	[124, 126, 128]
Pravastatin	Relatively hydrophilic statin; type I statin[c]	3T3-L1 adipocytes	No acceptor	[109]
Mevastatin (Compactin; 10 uM)	Relatively lipophilic statin; type I statin[c]	MPM	ApoA-I	[128]
Fatty acids and lipid membrane-disturbing agents				
Stimulation				
α-Linolenic acid conjugated to BSA	An omega-3 PUFA	THP-1	No acceptor	[67]
Cholesterol[b]		GM3468A normal human skin fibroblasts, primary cerebellar astroglia	ApoA-I	[129, 130]
Edelfosine[b] (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine)	An alkyl-phospholipid with amphiphilic properties	HepG2	No acceptor (the compound itself might perform as the acceptor)	[131]
Erucylphosphocholine ([(Z)-docos-13-enyl] 2-(trimethylazaniumyl)ethyl phosphate)	An alkyl-phospholipid with amphiphilic properties	HepG2	No acceptor (the compound itself might perform as the acceptor)	[131]
Miltefosine,[b] i.e. hexadecylphosphocholine (hexadecyl 2-(trimethylazaniumyl)ethyl phosphate)	An alkyl-phospholipid with amphiphilic properties	HepG2	No acceptor (the compound itself might perform as the acceptor)	[131]
Imipramine	An amphipathic amine	MPM	ApoA-I	[132]
Perifosine[b] (1,1-dimethylpiperidin-1-ium-4-yl) octadecyl phosphate	An alkyl-phospholipid with amphiphilic properties	HepG2	No acceptor (the compound itself might perform as the acceptor)	[131]
U18666A	An amphipathic amine	MPM	ApoA-I, HDL2	[132]
Inhibition				
1,2-dioleoyl-sn-glycero-3-phospho-rac-1-glycerol [a precursor of bis(monoacylglycero)phosphate (lysobisphosphatidic acid)]	Bis(monoacylglycero)phosphate (lysobisphosphatidic acid), a phospholipid highly abundant in the internal membranes of multivesicular late endosomes, in which it forms specialized lipid domains	RAW 264.7	Mβ-CD, ApoA-I, HDL	[133]
Cholesterol[b]		MPM	ApoA-I, HDL2	[132]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Edelfosine[b] (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine)	An alkyl-phospholipid with amphiphilic properties	THP-1	ApoA-I	[134]
Eicosapentaenoic acid [20:5(n-3)]	Omega-3 PUFA	RAW 264.7, THP-1	ApoA-I	[49, 135]
Linoleic acid	18:2 omega-6 PUFA	mBMDM	HDL	[136]
Miltefosine[b], i.e. hexadecylphosphocholine [hexadecyl 2-(trimethylazaniumyl)ethyl phosphate]	An alkyl-phospholipid with amphiphilic properties	THP-1	ApoA-I	[134]
Perifosine[b] (1,1-dimethylpiperidin-1-ium-4-yl) octadecyl phosphate	An alkyl-phospholipid with amphiphilic properties	THP-1	ApoA-I	[134]
Oleic acid (18:1)	Monounsaturated fatty acid	J774, RAW 264.7	ApoA-I	[49, 137]
Effectors of Akt, mTOR, PI-PLC				
Stimulation				
Akt1/2 kinase inhibitor	An inhibitor of Akt	BHK expressing ABCA1	ApoA-I	[138]
DEPC (10-[4′-(*N*,*N*-Diethylamino) butyl]-2-chlorophenoxazine hydrochloride)	An inhibitor of Akt; supresses mTORC1 activity	RAW 264.7, Min6, HepG2, BHK expressing ABCA1	ApoA-I	[138]
		BHK expressing ABCA1	Mβ-CD	[138]
Ku-0063794	mTOR inhibitor	ABCA1-expressing BHK cells	ApoA-I	[35]
LY294002	An inhibitor of PI3 kinase; supresses mTORC1 activity	HepG2, HEK293 expressing ABCA1, BHK expressing ABCA1	ApoA-I	[115, 138]
Rapamycin (at 10–100 nM; inhibition over 10 μM)	mTOR inhibitor	BHK expressing ABCA1	ApoA-I	[35, 138]
Torin-1	An inhibitor of mTORC1	BHK expressing ABCA1	ApoA-I	[138]
Inhibition				
PI-PLC	Hydrolyzes PIP2 to inositol triphosphate and diacylglycerol	RAW264.7, HEK293 expressing ABCA1	ApoA-I	[139]
Ceramide signaling				
Stimulation				
C_2-dihydroceramide	Ceramide analog that is not associated with apoptosis	CHO	ApoA-I	[140]
Ceramide	A lipid signaling molecule, a product of the digestion of sphingomyelin, an activator of cathepsin D (a lysosomal proteinase)	J774, CHO, CHO expressing ABCA1, HeLa expressing ABCA1	ApoA-I	[140, 141]
MAPP [(1S,2R)-D-erythro-2-(*N*-myristoylamino)-1-phenyl-1-propanol]	An inhibitor of alkaline ceramidase; elevates the level of endogenous ceramide	CHO	ApoA-I	[140]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
MAP kinase and non-receptor tyrosine kinase signaling				
Stimulation				
PD98059[b]	An inhibitor of MAP kinases MEK1 and MEK2	RAW 264.7, MPM	ApoA-I, HDL	[113, 142]
PP2 (i.e. AG 1879)	An inhibitor of Src family kinase	Jurkat cells (human acute T lymphocyte leukemia cell line)	ApoA-I	[143]
U0126	An inhibitor of MAP kinases ERK1/2	RAW 264.7, MPM	ApoA-I, HDL	[113, 142]
Inhibition				
AG490	Inhibitor of JAK-2	MAC-T	ApoA-I	[34]
PD98059[b]	An inhibitor of MAP kinases MEK1 and MEK2	MAC-T	ApoA-I	[34]
Raf1 kinase inhibitor I, i.e. GW5074 [3-(3,5-Dibromo-4-hydroxybenzyliden)-5-iodo-1,3-dihydroindol-2-one]	Inhibits signaling through the MAPK cascade	HEK293 expressing ABCA1	ApoA-I	[115]
Ion channels and Ca2 + regulation				
Stimulation				
BAY-K8644	An agonist of plasma membrane L-type Ca2 + channels	ABCA1-expressing BHK cells	ApoA-I	[44]
Digoxin	A cardioactive glycoside that inhibits Na +/K + ATPase, activates the mevalonate pathway, and stimulates the mitochondrial respiratory chain and synthesis of ATP	H9c2 (rat cardiomyocyte cell line)	No acceptor, ApoA-I	[144]
Ouabain	A cardioactive glycoside that inhibits Na +/K + ATPase, activates the mevalonate pathway, and stimulates the mitochondrial respiratory chain and synthesis of ATP	H9c2 (rat cardiomyocyte cell line)	No acceptor, ApoA-I	[144]
Nifedipine	A calcium channel blocker	RAW 264.7	ApoA-I, HDL	[145]
Inhibition				
BAPTA-AM	Intracellular Ca2 + chelator	ABCA1-expressing BHK cells, RAW 264.7	ApoA-I	[44]
Benzamil (stimulation at 100 uM)	Blocks the epithelial sodium channel and sodium-calcium exchange	MAC-T	HDL	[34]
Cyclosporine A	Calcineurin inhibitor	ABCA1-expressing BHK cells, RAW 264.7, THP-1	ApoA-I	[35, 44]
Disulphonic acid hydrate disodium salt	Chloride channel inhibitor	ABCA1-expressing BHK cells	ApoA-I	[44]
EDTA	Chelator of Ca2+	ABCA1-expressing BHK cells	ApoA-I	[44]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
EGTA	Chelator of Ca2+	ABCA1-expressing BHK cells, RAW 264.7	ApoA-I	[44]
Pimecrolimus	Calcineurin inhibitor	ABCA1-expressing BHK cells	ApoA-I	[35]
FK506 (tacrolimus)	Calcineurin inhibitor	ABCA1-expressing BHK cells, RAW 264.7	ApoA-I	[35, 44]
W-7	CaM antagonist (inhibits binding of Ca2+-bound CaM with its substrates)	ABCA1-expressing BHK cells	ApoA-I	[44]
Protein synthesis and degradation				
Stimulation				
ALLN (Calpain inhibitor I)	Thiol protease inhibitors; increases ABCA1 level; reversibly blocks Ca-dependent neutral cysteine protease calpain I	THP-1	ApoA-I	[146]
Bortezomib	A proteasome inhibitor	THP-1, RAW 264.7, MPM	ApoA-I, HDL	[147]
Chloroquine	A lysosomal inhibitor	HeLa expressing ABCA1	ApoA-I	[24]
Epoxomicin	A proteasome inhibitor	THP-1, RAW 264.7, MPM	ApoA-I, HDL	[147]
MG132	A proteasome inhibitor	THP-1, RAW 264.7, MPM	ApoA-I, HDL	[147]
Leupeptin	Thiol protease inhibitor; increases the ABCA1 level; inhibits serine and cysteine proteases (plasmin, trypsin, papain, calpain, and cathepsin B)	THP-1	ApoA-I	[146]
Pepstatin A	An inhibitor of cathepsin D, a lysosomal proteinase	mBMDM, MPM, J774, CHO	ApoA-I	[141]
Inhibition				
Brefeldin A	Lactone antibiotic that alters the structure and function of the Golgi apparatus; inhibits protein processing through the Golgi	J774, RAW 264.7, human skin fibroblasts, 3T3 L-1-derived adipocytes	ApoA-I (J774, adipocytes), ApoE4 (RAW 264.7), HDL (fibroblasts), HDL3 (J774)	[23, 28, 148]
Cycloheximide	Protein synthesis inhibitor	J774, MPM	ApoA-I	[29, 118]
Monensin	Polyether antibiotic that alters the structure and function of the Golgi apparatus; inhibits protein processing through the Golgi	RAW 264.7, human skin fibroblasts	ApoE4 (RAW 264.7), HDL (fibroblasts)	[36, 148]
Structural and trafficking proteins and their ligands				
Stimulation				
Colchicine	Inhibits microtubule polymerization, a metabolic and transport inhibitor, mitotic poison	Human skin fibroblasts	Plasma, albumin-depleted plasma, and ApoA-I-depleted plasma	[149]
Caveolin-1 expression	Integral membrane protein that acts as a scaffolding protein	HepG2 stably transfected caveolin-1	ApoA-I and plasma	[150]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
FGIN-1-27	A ligand for TSPO	THP-1	ApoA-I, HDL	[151]
Flunitrazepam	A ligand for TSPO	THP-1	ApoA-I	[151]
GGTI-298	An inhibitor of prenyltransferase GGTase-I that post-translationally modifies proteins for association to the membrane	mBMDM, THP-1	No acceptor, ApoA-I (mBMDM), HDL (mBMDM)	[152]
PK11195	A ligand for TSPO	THP-1	ApoA-I, HDL	[151]
DNA-depending processes				
Stimulation				
Etoposide (VP-16)	DNA topoisomerase II inhibitor	MPM	ApoA-I	[153]
Pyrrole-imidazole polyamide targeting ABCA1 promoter	A nuclease-resistant compound that inhibits the transcription factor by binding to the minor groove of DNA	RAW 264.7	ApoA-I	[154]
Teniposide (VM-26)	DNA topoisomerase II inhibitor	MPM	ApoA-I	[153]
Inhibition				
Mithramycin A	A chemotherapeutic drug that binds to GC-rich DNA sequences and blocks the binding of the transcription factor Sp1	RAW 264.7	ApoA-I	[155]
Other factors				
Stimulation				
Aspirin (up to 0.5 mM; inhibition over 1 mM)	NSAID and an antiplatelet drug (antiaggregant) used in CVD	RAW 264.7	ApoA-I	[63]
Doxazosin	α1-selective alpha blocker used to treat high blood pressure	RAW 264.7	ApoA-I	[154]
EP 80317	selective CD36 ligand	J774	ApoA-I, HDL	[156]
IRAK1 and IRAK4 inhibitor	IRAK1 participates in signaling via toll-like receptors/IL-1R	THP-1	ApoA-I, HDL	[157]
L. acidophilus bacteria strain K301, heat killed	A component of the human gut microflora; used as probiotics	THP-1	ApoA-I	[158]
Paraoxonase-1	An HDL-associated enzyme that contributes to the antioxidant and anti-inflammatory capacities of HDLs	J774, THP-1	No acceptor, HDL3, ApoA-I (J774)	[159]
		Fu5AH	HDL	[159]
Inhibition				
Arsenic trioxide	Chronic arsenic exposure is associated with an increased risk of CVD mortality	HepG2	HDL	[160]
Celecoxib	COX-2-specific inhibitor for the treatment of pain and inflammation	THP-1	ApoA-I	[161]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Chlamydia pneumoniae, viable	A Gram-negative obligate intracellular bacterium, a common cause of community-acquired pneumoniae	THP-1	ApoA-I	[162]
CRP	CRP in plasma are elevated in numerous disease states; CRP possesses proinflammatory and proatherogenic properties	THP-1, hPBMC	ApoA-I, HDL (THP-1)	[163]
D-(+)-trehalose 6,6′-dibehenate	Synthetic Clec4e (macrophage inducible Ca2+-dependent lectin) ligand	mBMDM	HDL, serum	[164]
HSP65	Binds to TCR and initiates immune responses, resulting in the production of proinflammatory cytokines	Jurkat cells (human acute T lymphocyte leukemia cell line), primary CD4+T cells	ApoA-I	[143]
JNJ-26854165 (serdemetan)	A proposed drug, activates p53	HEK293T; mantle cell lymphoma cell lines: MAVER-1, JeKo-1; multiple myeloma cell lines: OPM-2, U266	ApoA-I	[165]
Low pH (pH 5.5–6.5 compared with pH7.5)		hPBMC	ApoA-I, HDL2, human plasma	[166]
Low temperature		Human skin fibroblasts	Plasma, albumin-depleted plasma, and ApoA-I-depleted plasma	[149]
		RAW 264.7	ApoA-I, HSA	[167]
		mBMDM, primary hepatocytes	Mβ-CD	[168]
LPS (i.e. endotoxins)	A polysaccharide found in the outer membrane of Gram-negative bacteria that causes strong immune responses	MPM, THP-1	ApoA-I	[97, 169]
Okadaic acid	An inhibitor of protein phosphatases that downregulates caveolin expression	Fibroblasts, SMC	ApoA-I	[26]
PAPP-A	A metalloproteinase detected in ruptured atherosclerotic plaques	THP-1	ApoA-I, HDL	[50]
Ritonavir	A human immunodeficiency virus protease inhibitor	hPBMC, THP-1	ApoA-I, HDL (THP-1)	[170]
Trypsin (pretreatment of the cells)	A protease	J774	ApoA-I	[29]
Urotensin II	A vasoconstrictor peptide, a ligand of G protein-coupled receptor GPR14	THP-1	No acceptor	[171]
Vitamins, coenzymes and metabolites				
Stimulation				
9-nitro oleic acid	Found in human plasma; is generated by nitration of oleic acid by peroxynitrite and acidified nitrite	J774	HDL	[172]
Calcitriol [1,25-dihydroxyvitamin D3 or 1,25-(OH)2D3]	Hormonally active metabolite of vitamin D	THP-1	ApoA-I	[173]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Citrulline	A precursor of arginine and a byproduct of arginine oxidation by nitric oxide synthase	hPBMC, THP-1	ApoA-I, HDL	[174]
Coenzyme Q10	A component of the electron transport chain and a natural antioxidant	hPBMC, THP-1, J774	HDL	[175, 176]
Ethanol		Astrocytes, HepG2 (conditioned media)	ApoA-I, HDL, ApoE, conditioned medium	[32, 177]
GSH (glutathione)	A tripeptide, a thiol antioxidant	J774	HDL	[178]
Nicotinic acid (niacin)	Vitamin B3, lipid-lowering drug	MPM	HDL3	[179],
		3T3-L1 adipocytes	ApoA-I	[180]
Spermidine	Endogenous polyamine that induces autophagy	VSMC	ApoA-I	[181]
Inhibition				
7-Ketocholesterol (cholest-5-en-3beta-ol-7-one)	The major form of oxidized cholesterol that is present in oxidized LDL and atherosclerotic lesions	THP-1	ApoA-I	[182]
Acetoacetate	A component of ketone bodies	RAW 264.7	ApoA-I	[49]
Carbon monoxide	A component of the primary traffic emission; endogenously produced via heme degradation by heme oxygenase	J774	HDL	[183]
Glucose, increased level (20–25 mM)		RAW 264.7, human glomerular endothelial cells	ApoA-I	[126, 184]
Neopterin	A catabolic product of GTP, mainly synthesized by activated macrophages upon stimulation with IFNγ; a marker of inflammation	THP-1	ApoA-I, HDL	[185]
Extracts, components of plants and other natural sources, hits from small-molecule high-throughput screening				
Stimulation				
Alpinetin (7-hydroxy-5-methoxyflavanone)	A plant flavonoid abundantly present in Alpinia katsumadai Hayata	THP-1, hPBMC	ApoA-I or HDL	[186]
Anthocyanins (cyanidin-3-*O*-beta-glucoside and peonidin-3-*O*-beta-glucoside)	Plant pigments; phenolic compound rich in plants	MPM	ApoA-I	[73]
Arctigenin	Antioxidant, antitumor and anti-inflammatory substance from Arctium lappa plant	THP-1	ApoA-I, HDL2, HDL3	[187]
α-Asarone	Isolated from Purple perilla extract; known as a component of Acorus tatarinowii herb	J774	No acceptor	[188]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Astaxanthin	A carotenoid found in salmon, crab, and shrimp	RAW 264.7	ApoA-I, HDL	[189]
BCD1	A compound designed for ABCA1 induction based on the structure of rutaecarpine	RAW 264.7	HDL	[190]
Betulin	A pentacyclic triterpenoid from the bark of yellow and white birch trees	RAW 264.7	ApoA-I, HDL	[191]
Dihydrocapsaicin	A component of capsaicinoids of pepper	THP-1	ApoA-I	[192]
Chrysin	A flavonoid that is widely present in honey, propolis, and plant extracts	RAW 264.7	HDL	[75]
Curcumin	A polyphenol derived from the rhizome of turmeric (curcuma longa)	Adipocytes	ApoA-I	[193]
Dehydroxytrichostatin A (i.e. 9179B)	A compound found by screening of microbial secondary metabolites on the ability to induce ABCA1	RAW 264.7	ApoA-I	[194]
Diosgenin	A steroidal sapogenin present in a variety of plants, including fenugreek, yam root and soy bean	MPM, THP-1	ApoA-I	[195]
Emodin	Anthraquinone derivative from the roots of Rheum palmatum	THP-1	ApoA-I	[196]
Ethanolic extracts of Brazilian red propolis	Propolis, collected by honey bees from Dalbergia ecastophyllum (L) Taub. (Leguminosae)	THP-1	ApoA-I	[197]
Hesperetin	One of the major citrus flavonoids	THP-1	ApoA-I	[198]
Leoligin	The major lignan from edelweiss (Leontopodium nivale subsp. alpinum)	THP-1	ApoA-I, human plasma	[199]
Marrubium vulgare extract	The plant is widely used in traditional medicine; extract is rich in phenolic compounds	THP-1	HDL	[200]
Methyl protodioscin	A compound isolated from Dioscorea nipponica makino	THP-1, HepG2	ApoA-I	[78]
Nagilactone B	A novel compound, suppresses atherosclerosis in apoE −/− mice	RAW264.7	ApoA-I, HDL	[201]
Paeonol	A phenolic component purified from Paeonia suffruticosa (Cortex Moutan) used in traditional Chinese medicine	J774	ApoA-I	[202]
Phellinus linteus polysaccharide extract (at 5–20 μg/mL; inhibition at 100 μg/mL)	An immunomodulatory agent with a molecular weight of 153 Kd	THP-1	ApoA-I	[203]
Piperine	The pungent ingredient of black pepper	THP-1	ApoA-I, human plasma	[71]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Pomegranate peel polyphenols	Gallic acid, ellagic acid, punicalagins are the main active substances	RAW 264.7	ApoA-I	[204]
Protocatechuic acid	A metabolite of the flavonoid cyanidin-3-*O*-β-glucoside	MPM, THP-1	ApoA-I, HDL	[205]
Purple perilla extract	Contains rosmarinic acid, methyl rosmarinic acid, caffeic acid, chlorogenic acid and luteolin	J774	No acceptor	[188]
Rutaecarpine	A compound identified by screening of 20,000 compounds on the stimulation of the promoters of ABCA1 and CLA-1 (CD36 and lysosomal integral membrane protein II analogous 1)	RAW 264.7	ApoA-I, HDL	[206]
Quercetin	A natural flavonoid found in red wine, fruits and other natural sources with antioxidant, anti-inflammatory and anti-atherosclerosis activities	J774, THP-1, RAW 264.7	ApoA-I, HDL (J774, RAW 264.7)	[178, 207, 208]
Quercetin 7-O-sialic acid	Combines the cardioprotective effect of quercetin and *N*-acetylneuraminic acid	RAW 264.7	ApoA-I, HDL	[208]
Resveratrol	A stilbenoid with cardioprotective and anti-inflammatory properties	THP-1	Human plasma	[209]
Riccardin C	Non-sterol natural product isolated from liverworts	THP-1	ApoA-I, no acceptor	[77]
Sage (Salvia plebeia) weed extract	Contains antioxidants royleanonic acid, hispidulin and eupatorin	J774	No acceptor (just medium)	[210]
Saikosaponin A	One of the most active saikosaponins of Radix Bupleuri, a triterpenoid glycoside	THP-1	ApoA-I, HDL	[74]
Salvianolic acid B	A compound isolated from the Danshen root (Salvia miltiorrhiza Bunge)	THP-1	ApoA-I, HDL2, HDL3	[62]
Sesame oil	Oil from Sesamum indicum	MPM	ApoA-I	[211]
Sesamin	The most abundant lignan in sesame oil	RAW 264.7	HDL	[212]
Sesamol	A lignan found in sesame oil	MPM	ApoA-I	[211]
Tanshinone IIA	A lipophilic compound derived from Danshen (Salvia miltiorrhiza)	THP-1	ApoA-I, HDL	[213]
VAO-PE	Unsaponifiable fraction of the oil contains tocopherols, squalene, sterols (schottenol and spinasterol) and phenols (ferulic, syringic and vanillic acid)	THP-1	HDL, Ox-HDL pre-incubated with VAO-PE	[214]
Walnut oil	Walnuts contain high levels of PUFA, both linoleic acid and α-linolenic acid	THP-1	No acceptor	[67]

Table 1 (continued)

Substance used for cell treatment	Description of the substance	Cells[a]	Acceptor of cholesterol	References
Wogonin	A component of Scutellaria baicalensis Georgi extracts	J774	No acceptor	[215]
Zerumbone	A cyclic sesquiterpene isolated from Zingiber zerumbet Smith	THP-1	ApoA-I	[216]
Inhibition				
Cigarette smoke	Smoking a cigarette with a filter containing 14 mg of tar and 0.9 mg of nicotine was passed through 50 ml of culture medium	J774	HDL	[217]
Nicotine	Considered a pro-atherogenic component in tobacco	hPBMC	ApoA-I	[218]

ABC ATP-binding cassette, *ABCA1* ATP binding cassette subfamily A member 1, *ABCB1* ATP binding cassette subfamily b member 1, *ABCB4* ATP binding cassette subfamily B member 4, *ACAT* acyl-CoA cholesterol acyltransferase, *ACE* angiotensin converting enzyme, *ACE2* angiotensin-converting enzyme 2, *Akt* protein kinase B, *AMP* adenosine monophosphate, *AMPK* AMP-activated protein kinase, *APJ* apelin receptor, *apoA-I* apolipoprotein A-I, *apoA-II* apolipoprotein A-II, *ApoE* apolipoprotein E, *ATP* adenosine triphosphate, *BHK* baby hamster kidney cells, *BHK-21* baby hamster kidney cell line 21, *BLT* block lipid transport, *8-Br-cAMP* 8-bromoadenosine-cAMP, *CaM* calmodulin, *cAMP* adenosine 3′,5′-cyclic monophosphate, *CCL2* CC-chemokine ligand 2, *CHO* Chinese hamster ovary cells, *Clec4e* c-type lectin domain family 4 member E, *COX* cyclooxygenase, *COX-2* cyclooxygenase-2, *CRH* corticotropin-releasing hormone, *CRP* C-reactive protein, *CVD* cardiovascular disease, *CXCR2* C-X-C chemokine receptor type 2, *DPP-4* dipeptidyl peptidase 4, *DR3* death receptor 3, *EGF* epidermal growth factor, *ER* estrogen receptor, *ERK* extracellular signal–regulated kinase, *FGF-21* fibroblast growth factor 21, *GDP-15* growth differentiation factor-15, *GGTase-I* geranylgeranyltransferase type-I, *GLP-1* glucagon-like peptide 1, *GR* glucocorticoid receptor, *GTP* guanosine-5'-triphosphate, *HCAEC* primary human coronary artery endothelial cells, *HDL* high-density lipoprotein, *HEK293* human embryonic kidney 293 cells, *hPBMC* human peripheral blood mononuclear cells, *Huh7 cells* human hepatocellular carcinoma cell line, *HUVEC* human umbilical vein endothelial cells, *HSA* human serum albumin, *HSP65* heat shock protein 65, *ldlA-7* LDL receptor-deficient Chinese hamster ovary cells, *IFN* interferon, *IGF-1* insulin-like growth factor 1, *IL* interleukin, *IL-1R* IL-1 receptor, *IRAK1* interleukin-1 receptor-associated kinase 1, *IRAK4* inhibitor inhibitor of IL-1 receptor-associated kinase-4, *JAK* Janus kinase, *KO* knockout, *LDL* low-density lipoprotein, *LPL* lipoprotein lipase, *LPS* lipopolysaccharides, *LXR* liver X receptor, *MAC-T* immortalized bovine mammary secretory epithelial cells, *MAP* mitogen-activated protein, *Mβ-CD* methyl-β-cyclodextrin, hPBMC, mBMDM, MPM; [104]: DPP-4, GLP-1, *mBMDM* mouse bone marrow-derived macrophages, *MEK* mitogen-activated protein kinase kinase, *MPM* malignant pleural mesothelioma cells, *mTOR* mammalian target of rapamycin, *mTORC1* mammalian target of rapamycin complex 1, *NSAID* nonsteroidal anti-inflammatory drug, *Ox-HDL* oxidised HDL, *PAPP-A* pregnancy-associated plasma protein A, *PCSK9* proprotein convertase subtilisin/kexin type 9, *PI3* phosphoinositide-3, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PI-PLC* phosphatidylinositol-specific phospholipase C, *PKA* protein kinase A, *PLTP* phospholipid transfer protein, *PPAR* peroxisome proliferator-activated receptor, *PUFA* polyunsaturated fatty acid, *RAR* retinoic acid receptor, *RXR* retinoid X receptor, *SMC* smooth muscle cells, *SPTLC1* serine palmitoyltransferase long chain base subunit 1, *SR-B1* scavenger receptor class B member 1, *TCR* T-cell receptor, *TGF* transforming growth factor, *TNF* tumor necrosis factor, *TSPO* translocator protein, *VAO-PE* virgin argan oil phenolic extract, *VSMC* vascular smooth muscle cells

[a]In many cases, cells were treated with substances to differentiate to macrophages (e.g. by phorbol 12-myristate 13-acetate, macrophage colony-stimulating factor, or granulocyte/macrophage colony-stimulating factor), to induce expression of ABCA1 (e.g. by cpt-cAMP, TO-901317, or 22-OH + 9cRA), and transformed to foam cells (e.g. by Ac-LDL)

[b]The same factor stimulates and inhibits, depending on the cells, acceptor, and cholesterol depletion

[c]Statin description is given according to McFarland et al. [219]

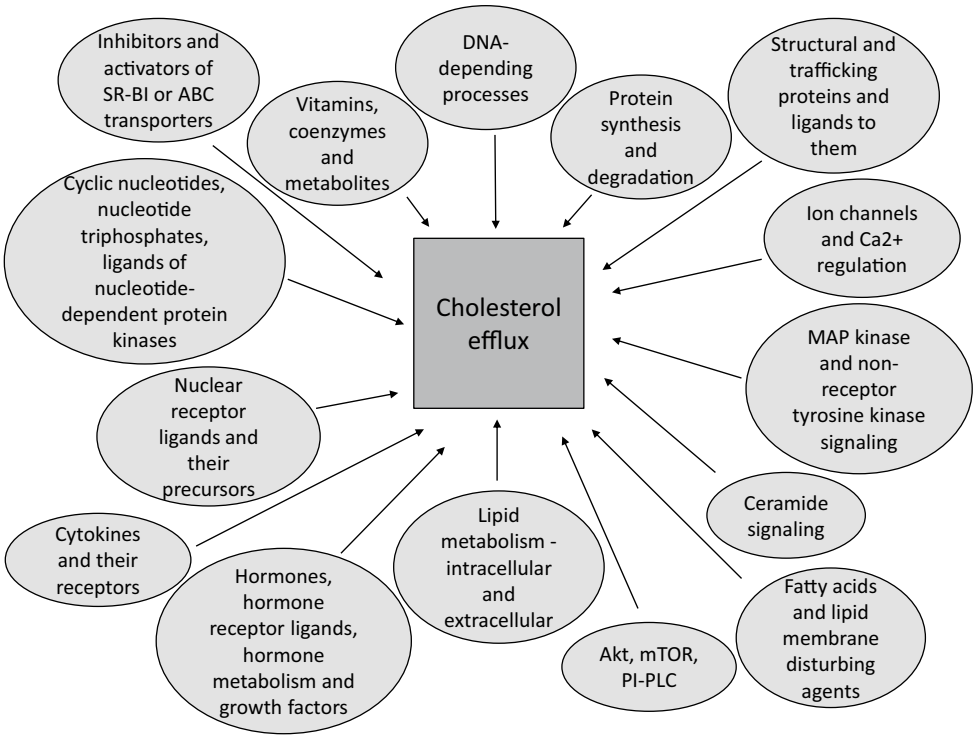

Fig. 1 Cholesterol efflux effectors grouped by signal and metabolic pathways. *ABC transporter* ATP-binding cassette transporter, *Akt/mTOR* protein kinase B/mammalian target of rapamycin, *MAP kinase* mitogen-activated protein kinase, *PI-PLC* phosphatidylinositol-specific phospholipase C, *SR-B1* scavenger receptor class B member 1

The distribution of activators and inhibitors between particular pathways is shown in Fig. 2. Importantly, the substances are distributed non-uniformly among different pathways; the 'biological oxidations' pathway includes mostly substances with an activating effect on cholesterol efflux (all-trans retinoic acid, ethanol, 17β-estradiol, progesterone, hydrocortisone, resveratrol), while signaling by the G protein-coupled receptor and protein tyrosine kinase 6 pathways include substances with an inhibiting effect (oleic and eicosapentaenoic acids). 'Biological oxidations' include biotransformation of xenobiotics and endogenous compounds in the liver, kidneys, gut and lungs. As far as chemicals that undergo functionalization, the electrophilic or nucleophilic species can be detrimental to biological systems. Electrophiles can react with electron-rich macromolecules such as proteins, DNA and RNA by covalent interaction, while nucleophiles have the potential to interact with biological receptors [221]. Thus, in addition to nuclear receptor ligands and their precursors activating cholesterol efflux and lipoprotein metabolism, and widely used in clinics (bezafibrate and fenofibric acid [222], pioglitazone [223], telmisartan [224]), targeting biological oxidation processes looks promising for the correction of inefficient reverse cholesterol transport in humans. For instance, the stimulating effect was described for chloroquine [225], diosgenin [226], 17β-estradiol [227], all-trans retinoic acid [228], ethanol [229], spermidine [230, 231], resveratrol [232] and 9-cis-retinoic acid [233].

3 Conclusions

We performed a comprehensive analysis of the various substances influencing cholesterol efflux, with pathway enrichment using the Reactome database. The activators and inhibitors of cholesterol efflux are non-uniformly distributed among different pathways. The substances influencing biological oxidation activate cholesterol efflux, and the substances influencing signaling by GPCR and PTK6 inhibit efflux. This analysis may be useful in the targeted therapy of structural and functional HDL deficiency.

Table 2 Substances and pathways influencing cellular cholesterol efflux (ChEBI and Reactome pathway indexes are included)

	R-HSA-112316 Neuronal System	R-HSA-381340 Transcriptional regulation of white adipocyte differentiation	R-HSA-1428517 The citric acid (TCA) cycle and respiratory electron transport	R-HSA-163685 Integration of energy metabolism	R-HSA-196854 Metabolism of vitamins and cofactors	R-HSA-211859 Biological oxidations	R-HSA-8978868 Fatty acid metabolism	R-HSA-400206 Regulation of lipid metabolism by PPAR-α	R-HSA-8957322 Metabolism of steroids	R-HSA-71291 Metabolism of amino acids and derivatives	R-HSA-446728 Cell junction organization	R-HSA-166520 Signaling by NGF	R-HSA-195721 Signaling by Wnt	R-HSA-2187338 Visual phototransduction	R-HSA-372790 Signaling by GPCR	R-HSA-5362517 Signaling by retinoic acid
Activator																
2981 Baicalin											•	•				
3086 Betulin												•	•			
3638 Chloroquine						•			•							
4551 Digoxin																
4629 Diosgenin						•										
4708 Doxazosin			•													
6426 Leupeptin												•				
15365 Aspirin																
15367 All-trans retinoic acid (tretinoin)			•		•	•								•		•
15940 Nicotinic acid (niacin)					•									•		
16236 Ethanol						•										
16243 Quercetin			•													
16469 17β-estradiol						•			•							
16610 Spermidine						•										
16856 GSH (glutathione)			•		•	•	•			•						
17026 Progesterone						•			•							
17351 α-Linolenic acid		•			•			•						•		
17579 All-trans β-carotene					•				•					•		
17650 Hydrocortisone (i.e. cortisol)						•			•							

Table 2 (continued)

	R-HSA-112316 Neuronal System	R-HSA-381340 Transcriptional regulation of white adipocyte differentiation	R-HSA-1428517 The citric acid (TCA) cycle and respiratory electron transport	R-HSA-163685 Integration of energy metabolism	R-HSA-196854 Metabolism of vitamins and cofactors	R-HSA-211859 Biological oxidations	R-HSA-8978868 Fatty acid metabolism	R-HSA-400206 Regulation of lipid metabolism by PPAR-α	R-HSA-8957322 Metabolism of steroids	R-HSA-71291 Metabolism of amino acids and derivatives	R-HSA-446728 Cell junction organization	R-HSA-166520 Signaling by NGF	R-HSA-195721 Signaling by Wnt	R-HSA-2187338 Visual phototransduction	R-HSA-372790 Signaling by GPCR	R-HSA-5362517 Signaling by retinoic acid
17823 Calcitriol						•										
18211 Citrulline												•				
23359 Colchicine																
27881 Resveratrol						•										
36062 Protocatechuic acid						•										
46245 Coenzyme Q10			•							•						
47499 Imipramine																
50122 Rosiglitazone		•		•				•							•	
50648 9-cis-retinoic acid					•	•								•		•
63892 Zerumbone																
65329 LY294002																
84612 cpt-cAMP											•					
Inhibitor																
8772 Raloxifene																
9635 Toremifene																
15344 Acetoacetate															•	
16196 Oleic acid				•	•					•				•	•	
16551 D-(+)-trehalose 6,6′-dibehenate																
17245 Carbon monoxide					•									•		
25675 Oligomycin																

Table 2 (continued)

	R-HSA-112316 Neuronal System	R-HSA-381340 Transcriptional regulation of white adipocyte differentiation	R-HSA-1428517 The citric acid (TCA) cycle and respiratory electron transport	R-HSA-163685 Integration of energy metabolism	R-HSA-196854 Metabolism of vitamins and cofactors	R-HSA-211859 Biological oxidations	R-HSA-8978868 Fatty acid metabolism	R-HSA-400206 Regulation of lipid metabolism by PPAR-α	R-HSA-8957322 Metabolism of steroids	R-HSA-71291 Metabolism of amino acids and derivatives	R-HSA-446728 Cell junction organization	R-HSA-166520 Signaling by NGF	R-HSA-195721 Signaling by Wnt	R-HSA-2187338 Visual phototransduction	R-HSA-372790 Signaling by GPCR	R-HSA-5362517 Signaling by retinoic acid
28364 Eicosapentaenoic acid		●						●			●				●	
30740 EGTA																
34159 15d-PGJ2							●									
38545 Rosuvastatin	●															
41423 Celecoxib							●									
41774 Tamoxifen						●										
41879 Dexamethasone																

	R-HSA-73887 Death receptor signaling	R-HSA-8848021 Signaling by PTK6	R-HSA-5619115 Disorders of transmembrane transporters	R-HSA-5663202 Diseases of signal transduction	R-HSA-5579029 Metabolic disorders of biological oxidation enzymes	R-HSA-5663084 Diseases of carbohydrate metabolism	R-HSA-168256 Immune system	R-HSA-174824 Plasma lipoprotein assembly, remodeling, and clearance	R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds	R-HSA-425397 Transport of vitamins, nucleosides, and related molecules	R-HSA-392499 Metabolism of proteins	R-HSA-400253 Circadian Clock	R-HSA-5653656 Vesicle-mediated transport	R-HSA-73857 RNA Polymerase II Transcription	R-HSA-8963743 Digestion and absorption
Activator															
2981 Baicalin				●											●
3086 Betulin				●									●		
3638 Chloroquine					●				●						
4551 Digoxin										●					
4629 Diosgenin															
4708 Doxazosin															

Table 2 (continued)

	R-HSA-73887 Death receptor signaling	R-HSA-8848021 Signaling by PTK6	R-HSA-5619115 Disorders of transmembrane transporters	R-HSA-5663202 Diseases of signal transduction	R-HSA-5579029 Metabolic disorders of biological oxidation enzymes	R-HSA-5663084 Diseases of carbohydrate metabolism	R-HSA-168256 Immune system	R-HSA-174824 Plasma lipoprotein assembly, remodeling, and clearance	R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds	R-HSA-425397 Transport of vitamins, nucleosides, and related molecules	R-HSA-392499 Metabolism of proteins	R-HSA-400253 Circadian Clock	R-HSA-5653656 Vesicle-mediated transport	R-HSA-73857 RNA Polymerase II Transcription	R-HSA-8963743 Digestion and absorption
6426 Leupeptin															
15365 Aspirin															
15367 All-trans retinoic acid (tretinoin)					•										
15940 Nicotinic acid (niacin)								•							
16236 Ethanol						•									
16243 Quercetin															•
16469 17β-estradiol					•										
16610 Spermidine									•						
16856 GSH (glutathione)															
17026 Progesterone					•	•									
17351 α-Linolenic acid			•					•		•		•		•	
17579 All-trans β-carotene															
17650 Hydrocortisone (i.e. cortisol)															
17823 Calcitriol					•										
18211 Citrulline															
23359 Colchicine							•								

Table 2 (continued)

	R-HSA-73887 Death receptor signaling	R-HSA-8848021 Signaling by PTK6	R-HSA-5619115 Disorders of transmembrane transporters	R-HSA-5663202 Diseases of signal transduction	R-HSA-5579029 Metabolic disorders of biological oxidation enzymes	R-HSA-5663084 Diseases of carbohydrate metabolism	R-HSA-168256 Immune system	R-HSA-174824 Plasma lipoprotein assembly, remodeling, and clearance	R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds	R-HSA-425397 Transport of vitamins, nucleosides, and related molecules	R-HSA-392499 Metabolism of proteins	R-HSA-400253 Circadian Clock	R-HSA-5653656 Vesicle-mediated transport	R-HSA-73857 RNA Polymerase II Transcription	R-HSA-8963743 Digestion and absorption
27881 Resveratrol															
36062 Protocatechuic acid	•														
46245 Coenzyme Q10															
47499 Imipramine									•						
50122 Rosiglitazone											•				
50648 9-cis-retinoic acid					•										
63892 Zerumbone	•														
65329 LY294002				•											
84612 cpt-cAMP															
Inhibitor															
8772 Raloxifene	•														
9635 Toremifene															
15344 Acetoacetate			•						•				•		
16196 Oleic acid			•							•	•				
16551 D-(+)-trehalose 6,6′-dibehenate															•
17245 Carbon monoxide															•

Table 2 (continued)

	R-HSA-73887 Death receptor signaling	R-HSA-8848021 Signaling by PTK6	R-HSA-5619115 Disorders of transmembrane transporters	R-HSA-5663202 Diseases of signal transduction	R-HSA-5579029 Metabolic disorders of biological oxidation enzymes	R-HSA-5663084 Diseases of carbohydrate metabolism	R-HSA-168256 Immune system	R-HSA-174824 Plasma lipoprotein assembly, remodeling, and clearance	R-HSA-425366 Transport of bile salts and organic acids, metal ions and amine compounds	R-HSA-425397 Transport of vitamins, nucleosides, and related molecules	R-HSA-392499 Metabolism of proteins	R-HSA-400253 Circadian Clock	R-HSA-5653656 Vesicle-mediated transport	R-HSA-73857 RNA Polymerase II Transcription	R-HSA-8963743 Digestion and absorption
25675 Oligomycin															
28364 Eicosapentaenoic acid											●	●		●	
30740 EGTA				●											
34159 15d-PGJ2															
38545 Rosuvastatin															
41423 Celecoxib															
41774 Tamoxifen															
41879 Dexamethasone		●										●			

GPCR G protein-coupled receptor, *NGF* nerve growth factor, *PPAR* peroxisome proliferator-activated receptor, black circle (●) denotes the action of a particular substance

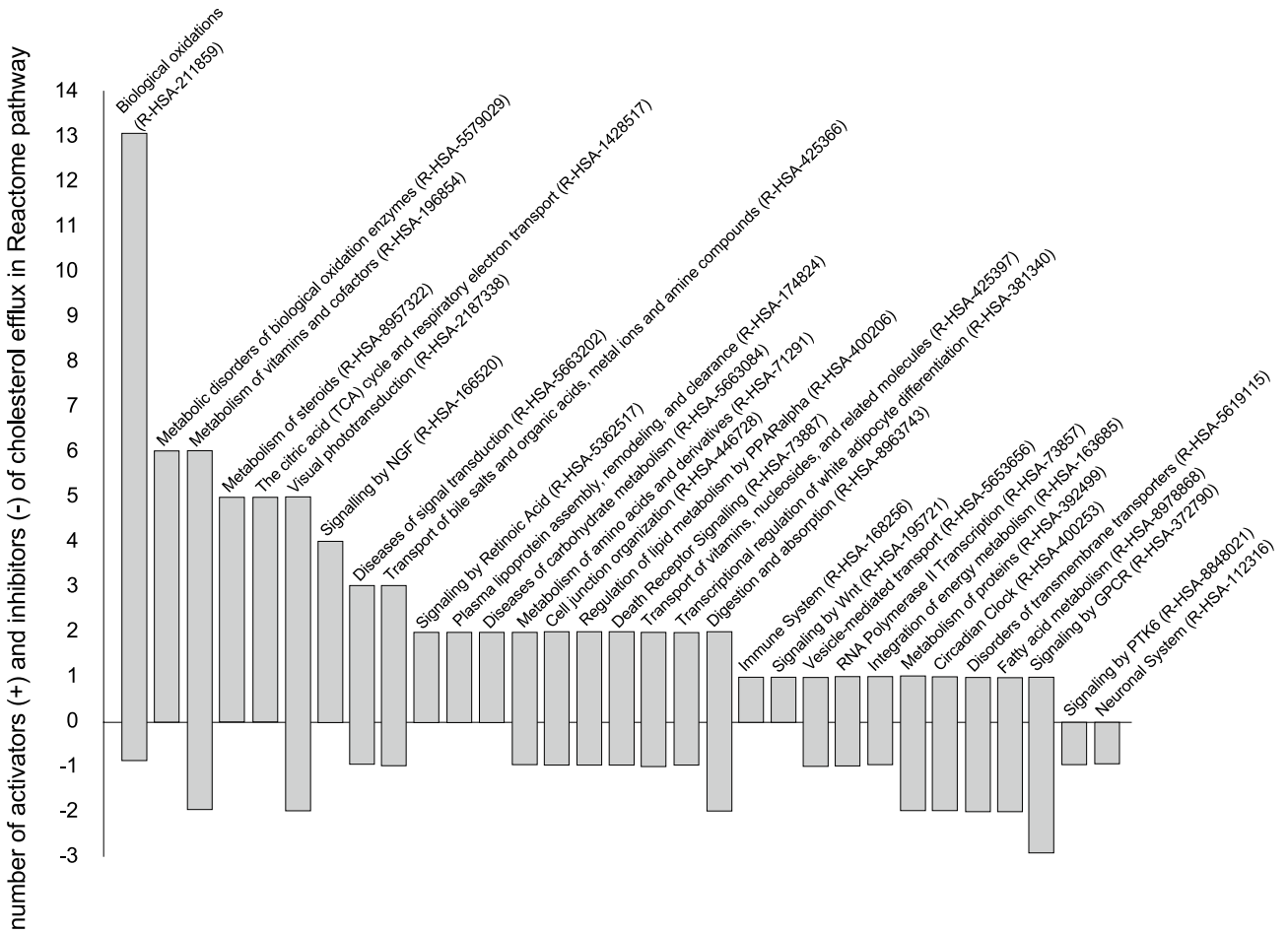

Fig. 2 The pathway-dependent distribution of activators and inhibitors in cholesterol efflux. The particular Reactome indexes are shown in brackets. *GPCR* G protein-coupled receptor, *NGF* nerve growth factor, *PPARalpha* peroxisome proliferator-activated receptor α, *PTK6* non-receptor tyrosine kinase, *Wnt* combination of Wg (wingless) and Int

Compliance with Ethical Standards

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Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

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