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Research review paper

Natural products as modulators of the nuclear receptors and metabolic sensors LXR, FXR and RXR

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ABSTRACT

Nuclear receptors (NRs) represent attractive targets for the treatment of metabolic syndrome-related diseases. In addition, natural products are an interesting pool of potential ligands since they have been refined under evolutionary pressure to interact with proteins or other biological targets.

This review aims to briefly summarize current basic knowledge regarding the liver X (LXR) and farnesoid X receptors (FXR) that form permissive heterodimers with retinoid X receptors (RXR). Natural product-based ligands for these receptors are summarized and the potential of LXR, FXR and RXR as targets in precision medicine is discussed.

1. Introduction

Metabolic syndrome-related diseases are major obstacles for the health systems worldwide. According to the World Health Organization (WHO) the prevalence of obesity has more than doubled between 1980 and 2014 with an overall 13% of the world's adult population being obese in 2014. The occurrence of overweight and obesity is not only an issue in high-income countries but also in urban settings of middle- and low-income countries, linking it globally to more deaths than underweight. The main cause for the increased occurrence of overweight and

Abbreviations: 6-ECDCA, 6α-ethyl-chenodeoxycholic acid (obeticholic acid); AA, arachidonic acid; ABC, ATP-binding cassette transporter; ACC, acyl-CoA carboxylase; AD, Alzheimer's disease; AF, activation function; ALS, amyotrophic lateral sclerosis; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; ANGPTL-4, angiopoietin-like protein 4; AP-1, activator protein 1; aP2, adipocyte fatty acid-binding protein-2; APO, apolipoprotein; AR, androgen receptor; ARL7, ADP-ribosylation factor-like 7; ASBT, apical sodium-dependent bile acid transporter; BAAT, bile acid CoA amino acid N-acetyltransferase; BACS, bile acid CoA synthase; BGP, Brazilian green propolis; BSEP, bile salt export pump; CA, cholic acid; CAR, constitutive androstane receptor; CAT, chloramphenicol acetyltransferase; CD, circular dichroism; CD36, scavenger receptor class B member 3; CDCA, chenodeoxycholic acid; CETP, cholesteryl ester transfer protein; COX-2, cyclooxygenase 2; CPT1A, carnitine palmitoyltransferase 1A; CRBPII, cellular retinol binding protein II; CREB, cAMP response element-binding protein; CRHF, *Cyperus rotundus* extract hexane fraction; CYP, cytochrome P450; D9k, calbindin D9k; DBD, DNA-binding domain; DCA, deoxycholic acid; DHA, docosahexaenoic acid; DR, direct repeat; EERP, ethanolic extracts of Brazilian red propolis; EGCG, Epigallocatechin-3-gallate; ELOVL6, fatty acid elongase 6; ER, estrogen receptor; ERK1/2, extracellular signal-regulated protein kinase 1/2; ETB, ethyl 2,4,6-trihydroxybenzoate; FABP3, fatty acid binding protein 3; FAS, fatty acid synthase; FCHL, familial combined hyperlipidemia; FGF, fibroblast growth factor; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; G6Pase, glucose-6-phophatase; GLUT4, glucose transporter 4; GR, glucocorticoid receptor; HDL, high density lipoprotein; HMGR, HMG-CoA reductase; HMOX-1, heme oxygenase-1; HNF4α, hepatocyte nuclear factor 4 α; HPLC-ESI-MS, high-performance liquid chromatography-electrospray ionization mass spectrometry; HSP27, heat shock protein 27; HTS, high-throughput screening; IBABP, ileal bile acid binding-protein; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; IR, inverted repeat; ITC, isothermal titration calorimetry; JNK1/2, c-Jun N-terminal kinase 1/2; LBD, ligand-binding domain; LCA, lithocholic acid; LDL, low density lipoprotein; LDLR, LDL receptor; LPL, lipoprotein lipase; LRH-1, liver receptor homolog-1; LXR, liver X receptor; MDR3, multidrug resistance protein 3; MR, mineralocorticoid receptor; MRP2/4, multidrug resistance-associated protein 2/4; MS, multiple sclerosis; Mylip/Idol, inducible degrader of the LDL receptor; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor κB; NMR, nuclear magnetic resonance; NPC1L1, Niemann-Pick C1-like protein 1; NR, nuclear receptor; NTCP, sodium taurocholate cotransporting polypeptide; Nur77, nuclear receptor subfamily 4 group A member 1 (nerve growth factor induced gene B); Nurr1, nuclear receptor subfamily 4 group A member 2 (Nur-related factor-1); OA, oleic acid; OATP, organic anion transporting polypeptide; OSTα/β, organic solute transporter α/β; PBC, primary biliary cirrhosis; PEPCK, phosphoenolpyruvate carboxykinase; PLTP, phospholipid transfer protein; PPAR, peroxisome proliferator-activated receptor; PR, progesterone receptor; PUFAs, polyunsaturated fatty acids; PXR, pregnane X receptor; Q3GA, quercetin-3-*O*-glucuronide; RA, retinoic acid; RAR, retinoic acid receptor; RC, Riccardin C; RCT, reverse cholesterol transport; RE, response element; RF, Riccardin F; ROR, RAR-related orphan receptor; RVS, *Rhus verniciflua* Stokes; RXR, retinoid X receptor; SBARM, selective bile acid receptor modulator; SCD-1, stearoyl-CoA desaturase-1; SHP, small heterodimer partner; SNP, single nucleotide polymorphism; SNuRMs, selective NR modulators; SOAE, aqueous extract of sesame oil; SPR, surface plasmon resonance; SR-A, scavenger receptor class A; SR-BI, scavenger receptor class B type I; SRC-1/2/3, steroid receptor coactivator-1/2/3; SREBP-1c, sterol regulatory element binding protein-1c; SRXRMs, selective RXR modulators; SULT2A1, sulfotransferase 2A1; SUMO, small ubiquitin-like modifier; TG, triglyceride; TICE, transintestinal cholesterol efflux; TLR, Toll-like receptor; TR, thyroid hormone receptor; TR-FRET, time-resolved fluorescence resonance energy transfer; TRPV6, transient receptor potential vanilloid 6; UC, ulcerative colitis; UGT2B4, UDP-glucuronosyltransferase family 2 member B4; VDR, vitamin D receptor; VLDL, very low density lipoprotein; WBM, white button mushroom; WHO, World Health Organization

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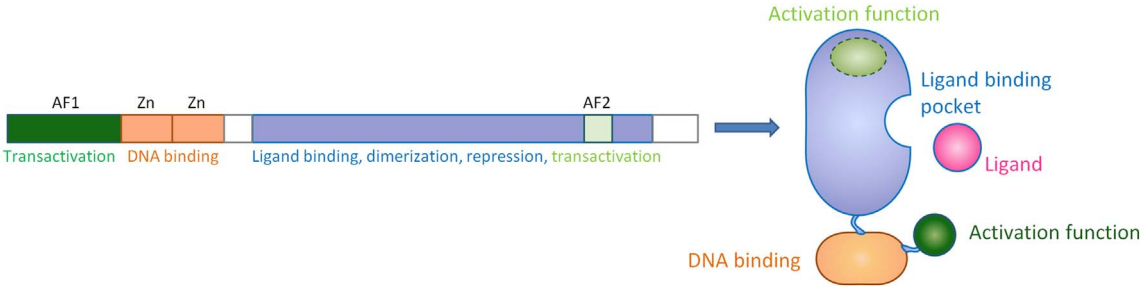


Fig. 1. Structural organisation of nuclear receptors. Most nuclear receptors typically consist of several domains: an N-terminal region with a ligand-independent activation function (AF1) important for the interaction with coregulators as well as other transcription factors, a highly conserved zinc-finger DNA-binding domain (DBD), which allows the receptor to bind specific response elements (RE), a variable hinge-domain, a ligand-binding domain (LBD) with a ligand-dependent activation function (AF2), and a highly variable C-terminal domain.

obesity lies in the enhanced consumption of energy-dense, high-fat foods and an increase in sedentary lifestyles, resulting in an imbalance between energy consumption and expenditure. Overweight and obesity can be seen as gateway conditions facilitating the development of more serious diseases, including diabetes and cardiovascular diseases (WHO, 2016).

Nuclear receptors are ligand-activated transcription factors that regulate target gene expression in a wide variety of physiological pathways such as metabolic processes (Degirolamo et al., 2015; Gronemeyer et al., 2004; Mangelsdorf and Evans, 1995).

Nuclear receptors involved in metabolism are classified as type 2 nuclear receptors, which are located in the nucleus regardless of ligand binding. With no ligand present, they are bound to the response elements (REs) of target genes together with corepressors. Upon ligand binding, conformational changes lead to the dissociation of these corepressors and to their exchange with coactivators, leading to the initiation of target gene expression (Mangelsdorf and Evans, 1995). Fig. 1 depicts the structural organisation of nuclear receptors. Most type 2 nuclear receptors form heterodimers with the retinoid X receptors (RXRs, NR2B1/NR2B2/NR2B3) (Sever and Glass, 2013). Type 2 nuclear receptors for the regulation of metabolic processes include the liver X receptors [LXRα (NR1H3) and LXRβ (NR1H2)], the farnesoid X receptor (FXR, NR1H4), the peroxisome proliferator-activated receptors (PPARs, NR1C1/NR1C2/NR1C3), and the RXRs. Ligands for these receptors include fatty acids, oxysterols and bile acids as well as rexinoids, pointing to their relevance in the regulation of metabolic pathways (Chawla et al., 2001; Janowski et al., 1996; Keller et al., 1993; Parks et al., 1999) (Fig. 2).

Metabolic nuclear receptors are important regulators in lipid and glucose metabolism. Disturbances in these metabolic processes are major underlying causes for metabolic syndrome-related diseases. Thus, modulating the activation of these nuclear receptors is of interest in drug discovery and development.

Natural products are a diverse and interesting source for the discovery of new lead structures (Newman and Cragg, 2016). After a successful era of natural product research, many pharmaceutical companies stopped their investment in natural product-driven drug discovery in the 1990s. The reason behind this step were the advantages of combinatorial synthesis and high-throughput screening (HTS) of chemical libraries over natural product libraries (Koehn and Carter, 2005; Li and Vederas, 2009; Shen, 2015). Major obstacles in HTS of natural product libraries arise from their heterogeneity and complexity. Hits obtained from extracts need to be purified normally guided by biological assays in order to identify the active constituents. Furthermore, the concentrations of the individual components of a mixture are not known. If an active compound is only present in trace amounts, it might not be detected via HTS, whereas if it is present in very high amounts, it might interfere with or perturb the assay. Another major disadvantage of natural products is that their supply can be limited either because the availability of the source is limited or because the synthesis is not feasible. A further drawback of natural products is that the isolation and purification of the active compound can be very difficult, especially if the target compound constitutes less than 1% of the weight of the extract (Koehn and Carter, 2005).

Notably, natural product research has gained new attention in recent years, as several technological advances helped to overcome many

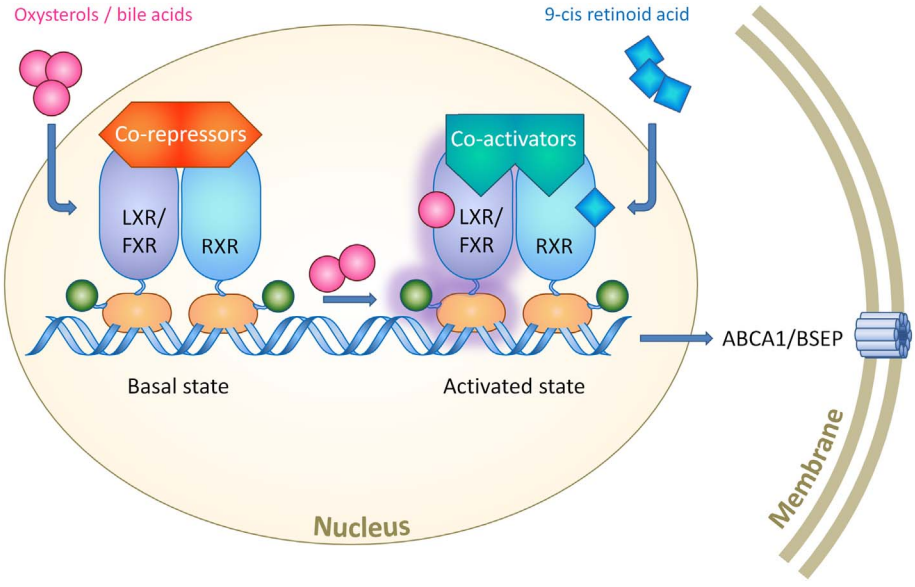


Fig. 2. Mechanism of action of nuclear receptors. The liver X receptor (LXR) or farnesoid X receptor (FXR) forms a heterodimer with the retinoid X receptor (RXR) that is bound to the response element (RE) on the DNA in the basal state. Corepressors are bound to the heterodimer complex in the basal state thereby repressing target gene expression. Upon ligand binding to LXR, FXR or RXR, conformational changes lead to the exchange of corepressors with coactivators resulting in an activated state. This results in the expression of target genes like ATP-binding cassette transporter A1 (ABCA1) for LXR or bile salt export pump (BSEP) for FXR.

of the above mentioned disadvantages of natural product research (Koehn and Carter, 2005; Li and Vederas, 2009; Shen, 2015). For instance, the identification and structure elucidation of unknown compounds is facilitated by high-performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-ESI-MS) and by advances in high-resolution nuclear magnetic resonance (NMR) technologies (Koehn and Carter, 2005; Li and Vederas, 2009; Strege, 1999). In some HTS assays, the problem of light-scattering interferences or fluorescing compounds can be resolved by lifetime discriminated polarization or by simply raising the concentration of the fluorophore (Fowler et al., 2002; French et al., 1998; Koehn and Carter, 2005; Turek-Etienne et al., 2003). Developments in the field of metabolic engineering and microbial cultivation as well as advances in genetic methods help to solve the "supply problem" of natural products and hold promise for the development of natural product-derived drugs (Khosla and Keasling, 2003; Koehn and Carter, 2005; Ling et al., 2015; Shen, 2015).

Natural products have chemically diverse structures that differ from synthetic and combinatorial compounds in several aspects. In general, they are sterically more complex than their synthetic counterparts, have a higher molecular weight and they incorporate more oxygen atoms than synthetics but less nitrogen, halogen and sulphur atoms. Moreover, natural products contain more fused, bridged or spiro ring systems than combinatorial compounds and they usually have a higher amount of solvated hydrogen-bond donors and acceptors in comparison to combinatorial compounds (Feher and Schmidt, 2003; Henkel et al., 1999; Koehn and Carter, 2005; Lahlou, 2013).

Natural products do not only show structural and chemical diversity, but also biodiversity and profuse functionality (Jones et al., 2006; Koehn and Carter, 2005; Shen, 2015). They are often viewed as so-called privileged structures (Evans et al., 1988) as they are capable of interacting with multiple proteins or other biological targets (Koehn and Carter, 2005; Lahlou, 2013; Shen, 2015). They have been produced in living systems where they have been refined under evolutionary pressure and a large portion of natural products has advantageous pharmacokinetic properties (Feher and Schmidt, 2003; Firn and Jones, 2003; Jones et al., 2006; Koehn and Carter, 2005; Lam, 2007; Wink, 2003). Even if a natural product itself cannot be used as a therapeutic drug due to supply problems, for cost reasons or unfavorable bioavailabiliy, it may help to understand the interaction with a specific target or it may be used as a lead for synthetic mimetics (Koehn and Carter, 2005). Moreover, studying their pharmacological profile may deliver scientific knowledge for ethnopharmacologically used products.

This review focuses on the nuclear receptors LXR, FXR, and RXR, their influence on metabolism and their potential as therapeutic targets.

At this point it needs, however, to be mentioned that most *in vivo* studies regarding the herein discussed nuclear receptors were performed in rodents, especially in mice. Due to the significant differences in metabolism in mice and humans, not all results are translatable between these species and have to be interpreted with caution (Schaap et al., 2014). One major difference between mouse and human metabolism is, for example, that mice lack cholesteryl ester transfer protein (CETP), which, in humans, is responsible for the transfer of cholesteryl esters from high density lipoprotein (HDL) to lipoproteins that contain apolipoprotein (APO) B, like low density lipoprotein (LDL) and very low density lipoprotein (VLDL) (Guyard-Dangremont et al., 1998). This might also be the reason why mice transport the majority of cholesterol in HDL, whereas humans carry most cholesterol in LDL (Bergen and Mersmann, 2005; Camus et al., 1983; Vitic and Stevanovic, 1993).

Taking a closer look on LXR, there are some striking differences in the regulation of target genes in rodents versus humans. In mice and rats, the expression of the cytochrome P450 7A1 (CYP7A1), which promotes the rate-limiting step in the conversion of cholesterol to bile acids (Russell and Setchell, 1992), can be regulated by LXR. It was shown that the mouse and rat CYP7A1 promoter contain an LXRE, whereas this does not hold true for humans, meaning that the CYP7A1 promoter cannot be stimulated by LXR (Agellon et al., 2002; Chen et al., 1999; Chiang et al., 2001; Goodwin et al., 2003; Lehmann et al., 1997; Peet et al., 1998). Moreover, CETP, which is not present in mice, is regulated by LXR in humans (Luo and Tall, 2000).

In regard to FXR, differences in bile acid composition and metabolism are of particular importance. Besides differences in the regulation of bile acid synthesis and conjugation, the bile acid pool in humans is compared to mice more hydrophobic (Chiang, 2009; Heuman, 1989; Russell, 2003; Sanyal et al., 2007). This is particularly relevant because hydrophobic bile acids are good agonists of FXR (Ding et al., 2015). The bile acid pool in mice consists of hydrophilic bile acids like cholic acid (CA) and α-, β- and ω-muricholic acid, which are almost exclusively conjugated with taurine (de Aguiar Vallim et al., 2013). In humans, 40% of the bile acid pool consists of CA, additional 40% of the hydrophobic bile acid chenodeoxycholic acid (CDCA) and 20% of the also hydrophobic deoxycholic acid (DCA) (Li and Chiang, 2014). Interestingly, taurine conjugated α- and β-muricholic acid were identified to be antagonists of FXR (Sayin et al., 2013).

Natural products as modulators of these receptors will cover a major part of the review. The possible importance of precision medicine in the context of these nuclear receptors and the therapy of metabolic syndrome-related diseases is finally discussed. For PPARs we refer to several recent reviews giving comprehensive overviews regarding this topic (Gross et al., 2017; Rigano et al., 2017; Wang et al., 2014).

2. The liver X receptor (LXR)

The liver X receptor exists in two isoforms, LXRα and LXRβ. LXRα (also known as NR1H3) is expressed in metabolically active tissues, like the liver, adipose, kidney, macrophages and intestines, whereas LXRβ (or NR1H2) is expressed ubiquitously (Apfel et al., 1994; Repa and Mangelsdorf, 2000; Willy et al., 1995).

As type 2 nuclear receptors, LXRs form heterodimers with RXR. These heterodimers belong to the so-called permissive heterodimers, meaning that the receptor dimer can be activated either by ligands for LXR or RXR, or even by both synergistically (Willy et al., 1995).

Endogenous ligands of the LXR/RXR heterodimer are oxysterols, which are oxygenated derivatives of cholesterol and intermediate metabolites of cholesterol biosynthesis (Janowski et al., 1999; Janowski et al., 1996; Schroepfer Jr, 2000). Ligand activation of LXR leads to the recruitment of specific coactivators (e.g. steroid receptor coactivator-1 (SRC-1)), which, for instance, induce a change in local chromatin architecture *via* histone acetylation, finally resulting in the transcription of target genes (Janowski et al., 1999; Wagner et al., 2003).

LXRs are physiological regulators of cholesterol and lipid metabolism and influence glucose metabolism. In addition, they have been shown to repress transcription of certain pro-inflammatory genes (Jakobsson et al., 2012; Ogawa et al., 2005; Terasaka et al., 2005). Thus, LXRs can either activate or repress gene expression (Joseph et al., 2003).

2.1. The role of LXR in metabolic processes

2.1.1. Regulation of cholesterol homeostasis

A stringent control of systemic and cellular cholesterol levels is important for physiological homeostasis. Although cholesterol is essential for mammalian cells, excess cholesterol is toxic and contributes to the development of cardiovascular disease (Bonamassa and Moschetta, 2013; Brown and Yu, 2009; Hong and Tontonoz, 2014).

There are two pathways for the excretion of cholesterol: the biliary reverse cholesterol transport (RCT) and the non-biliary RCT, also termed transintestinal cholesterol efflux (TICE) (Brown et al., 2008; Glomset, 1968; van der Velde et al., 2007; Vrins, 2010). Notably, LXRs are master regulators of reverse cholesterol transport and have therefore a unique role in cholesterol homeostasis.

The hepatobiliary RCT was considered as the only significant route

for cholesterol elimination from the body, until it was observed that part of the cholesterol found in feces does not derive from bile or diet, but originates from TICE, presenting a non-biliary pathway for RCT *via* the small intestines (Miettinen et al., 1981; Pertsemlidis et al., 1973; van der Velde et al., 2007). TICE is less well-understood compared to the biliary RCT route.

One of the first direct LXR target genes identified was ATP-binding cassette transporter A1 (ABCA1) (Costet et al., 2000; Venkateswaran et al., 2000). LXR activation leads to a robust upregulation of ABCA1 in macrophages as well as in the intestine and in the liver (Kannisto et al., 2014; Plosch et al., 2002; Repa et al., 2000b). In intestinal enterocytes and in hepatocytes, ABCA1 is located in the basolateral membrane (Murthy et al., 2002; Neufeld et al., 2002; Ohama et al., 2002). As ABCA1 is responsible for the efflux of cholesterol to APOA1 which results in the formation of HDL, the intestine and the liver are important sources of HDL (Basso et al., 2003; Brunham et al., 2006).

Another transporter that promotes cholesterol efflux from macrophages, which is also an LXR target gene, is ABCG1. Current knowledge suggests that ABCG1 is an intracellular transporter that promotes cholesterol transfer to mature HDL, thereby complementing ABCA1 function (Kennedy et al., 2001; Tarling and Edwards, 2011; Wang et al., 2004).

Moreover, it has been shown that in the intestine, activation of LXR enhances fecal sterol excretion *via* upregulation of the transporter heterodimer ABCG5/G8 (van der Veen et al., 2009; Yasuda et al., 2010). This ABC transporter heterodimer is located in the apical membrane of intestinal enterocytes (Klett et al., 2004) and it has been shown that both genes are target genes of LXR, although they do not contain an LXR response element (Berge et al., 2000; Repa et al., 2002). The transporter heterodimer ABCG5/G8 can further be found in the canalicular (apical) membrane of hepatocytes, where it is responsible for the efflux of cholesterol into the bile. ABCG5 and ABCG8 are, like in the intestine, upregulated by activation of the liver X receptor, whereby biliary cholesterol secretion is enhanced (Graf et al., 2003; Klett et al., 2004; Repa et al., 2002; Yu et al., 2002).

In the intestine, LXR further limits cholesterol absorption by downregulating Niemann-Pick C1-like protein 1 (NPC1L1) (Duval et al., 2006). NPC1L1 is, like ABCG5/G8, located in the apical membrane of enterocytes and has a major role in cholesterol uptake from the intestinal lumen (Altmann et al., 2004; Davis et al., 2004). In the liver, NPC1L1 is located in the canalicular membrane of hepatocytes, facilitating the uptake of cholesterol from bile (Temel et al., 2007). The transcriptional control of NPC1L1 is still not completely understood.

Moreover, LXRs also regulate the expression of proteins involved in lipid remodeling such as CETP (Luo and Tall, 2000), phospholipid transfer protein (PLTP) (Laffitte et al., 2003b) and lipoprotein lipase (LPL) (Zhang et al., 2001). Among the LXR target genes are the gene cluster of apolipoproteins E, C1, C2 and C4 (APOE, APOC1, APOC2 and APOC4), which are implicated in lipid transport and catabolism, thus further highlighting the role of LXR in lipid homeostasis (Calkin and Tontonoz, 2012; Laffitte et al., 2001; Mak et al., 2002).

2.1.2. Regulation of fatty acid homeostasis

LXRs are key regulators of fatty acid and triglyceride homeostasis. They are implicated in (hepatic) lipogenesis, as their activation results in an upregulation of sterol regulatory element binding protein (SREBP)-1c, which is a master hub in *de novo* fatty acid synthesis (Repa et al., 2000a). *Via* SREBP-1c, LXRs can increase the expression of the lipogenic enzymes stearoyl-CoA desaturase-1 (SCD-1), acyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) (Bennett et al., 1995; Lopez et al., 1996; Tabor et al., 1999; Yoshikawa et al., 2001). FAS and SCD-1 are not only indirectly regulated by LXR *via* SREBP-1c, but due to LXRE in the promoter of their genes they can be directly induced by LXR ligands (Chu et al., 2006; Joseph et al., 2002). As excess free cholesterol is toxic, it seems reasonable that high levels of cholesterol lead to the synthesis of fatty acids *via* LXR, which are then used for the esterification of cholesterol (Calkin and Tontonoz, 2012).

2.1.3. Influence on glucose homeostasis

LXRs have an impact on glucose homeostasis, yet the results from the corresponding studies are somewhat contradictory.

Laffitte et al. showed that treatment of insulin-resistant, obese mice with an LXR agonist improved glucose tolerance *via* an alteration of gene expression in both liver and adipose tissue (Laffitte et al., 2003a). LXRβ, but also LXRα (although at lower levels) is expressed in human pancreatic beta cells (Chuang et al., 2008) and is responsible for an increase of both basal and stimulated insulin secretion upon activation (Efanov et al., 2004; Ogihara et al., 2010).

In contrast, other studies showed that LXR-deficient mice have improved glucose tolerance (Kalaany et al., 2005) and ob/ob mice that are deficient of LXRs exhibited improved insulin sensitivity in comparison to those possessing LXRs (Beaven et al., 2013).

2.1.4. LXR and inflammation

Activation of LXR contributes to an anti-inflammatory response *via* diverse mechanisms as reviewed previously (Im and Osborne, 2011; Tall and Yvan-Charvet, 2015). The most direct effect of LXR appears to be the transrepression of pro-inflammatory target genes induced *via* transcription factors that are activated through Toll-like receptor (TLR) 4 signaling, such as nuclear factor κB (NF-κB) or activator protein 1 (AP-1) (Joseph et al., 2003; Tall and Yvan-Charvet, 2015). The current view suggests that ligand-activated LXRs are conjugated to a small ubiquitin-like modifier (SUMO) protein. SUMOylated LXR monomers then bind to and stabilize repressive nuclear complexes bound to promoters (but not to LXRE) of pro-inflammatory target genes (Ghisletti et al., 2007; Tall and Yvan-Charvet, 2015). LXRs thereby inhibit the expression of inflammatory mediators like inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2 and interleukin 6 (IL-6) (Joseph et al., 2003). A recent study emphasizes an important role of the LXR target gene ABCA1 for the anti-inflammatory effect of LXR by redistributing membrane cholesterol and thus disrupting TLR signaling (Ito et al., 2015). As inflammation promotes the development of atherosclerosis, it is likely that the anti-inflammatory activities of LXRs contribute to their beneficial effects in atherosclerosis (Glass and Witztum, 2001; Lusis, 2000).

2.2. LXR as therapeutic target

The fact that LXR plays an important role in the regulation of cholesterol and lipid metabolism, as well as in the inflammatory response, is of relevance for drug development in metabolic diseases like atherosclerosis, diabetes mellitus type II, and nonalcoholic fatty liver disease (Jakobsson et al., 2012).

Synthetic agonists of both LXRα and LXRβ like T0901317 (Schultz et al., 2000) and GW3965 (Collins et al., 2002) have been developed in the early 2000s. These compounds are frequently used in experimental studies, yet cannot be used therapeutically due to side effects like hypertriglyceridemia and liver steatosis (Joseph et al., 2002; Lund et al., 2006). The reason for these elevated serum triglyceride levels and liver triglyceride contents is that LXR activation leads to the transcription of SREBP-1c (Repa et al., 2000a). SREBP-1c is a master hub in *de novo* fatty acid synthesis, regulating the transcription of all the genes involved in this process (Shimomura et al., 1998). A possible strategy to overcome this obstacle would be the selective targeting of LXRβ, since LXRα is the predominant isoform in the liver and therefore thought to be responsible for SREBP-1c expression in the liver (Calkin and Tontonoz, 2012). In the last decade, a few compounds with at least partial selectivity for LXRβ have been developed (Ratni et al., 2009), though developing LXRβ-selective agonists is hampered due to the sequence similarity of the ligand-binding domains of the two LXR isoforms (Janowski et al., 1999). Another possibility to avoid the development of liver steatosis would be the development of tissue-selective

LXR agonists. The intestine-specific LXR agonist GW6340 causes an upregulation of LXR target genes in the intestine, but not in the liver, and further promotes macrophage reverse cholesterol transport (Yasuda et al., 2010).

LXR antagonists or inverse agonists might be beneficial in the treatment of hypertriglyceridemia and hepatic steatosis, possibly also in nonalcoholic fatty liver disease (NAFLD). Though there are studies suggesting that LXR agonists are capable of reducing inflammation in NAFLD (Wouters et al., 2010), it has been shown that the LXR inverse agonist SR9238 reduces hepatic inflammation, liver steatosis and fibrosis in ob/ob mice on a high-fat, high-fructose and high-cholesterol diet (Griffett et al., 2015).

The quest for LXR modulators suitable for the treatment of metabolic diseases is still ongoing. Natural products with a putative reduced potency and side effects or with a tissue- or subtype-selective activity may be suitable approaches.

2.3. Natural product-derived ligands for LXR

Endogenous agonists for LXRs include oxysterols, which are oxygenated derivatives of cholesterol (Janowski et al., 1996; Schroepfer Jr, 2000). These oxysterols include 22(*R*)-hydroxycholesterol, 24(*S*)-hydroxycholesterol and 24(*S*),25-epoxycholesterol (Table 1), which are capable of activating both LXR isoforms, LXRα and LXRβ (Forman et al., 1997; Janowski et al., 1996; Lehmann et al., 1997; Schroepfer Jr, 2000). Oxysterols, however, can next to their endogenous production, also be taken up *via* the diet (Leonarduzzi et al., 2002; Schroepfer Jr, 2000).

Besides agonists, there also exist endogenous LXR ligands with antagonistic activity. Polyunsaturated fatty acids (PUFAs), like arachidonic acid (Table 1), have been identified as competitive antagonists of LXR (Kuang et al., 2012; Ou et al., 2001; Yoshikawa et al., 2002). Berrodin et al. identified 5α,6α-epoxycholesterol (Table 1), which can be found endogenously as well as in processed foods, as a ligand of both LXR isoforms (Berrodin et al., 2010; Leonarduzzi et al., 2002). Interestingly, they showed that 5α,6α-epoxycholesterol can either act as an agonist, antagonist or inverse agonist, depending on the cell context and target genes (Berrodin et al., 2010).

Phytosterols from the 4-desmethyl family, which are naturally occurring analogues of cholesterol, are able to reduce serum cholesterol levels in humans (Moghadasian and Frohlich, 1999). This effect is, in part, due to the competition of phytosterols with cholesterol for the solubilization into micelles and therefore reduced cholesterol absorption (Ikeda et al., 1988). Plat et al. showed that there is a second, distinct mechanism, by which phytosterols cause a reduction of serum cholesterol levels, namely LXR activation. They showed that both LXRα and LXRβ are activated in Caco-2 cells upon phytosterol treatment, and that ABCA1 mRNA expression is increased (Plat et al., 2005). Interestingly, Hoang et al. found that fucosterol (Table 1), a sterol present in marine algae, does not induce accumulation of triglycerides in hepatocytes, despite the activation of both LXR isoforms at 100 μM (Hoang et al., 2012b).

Paxilline (Table 1), a non-oxysterol natural product derived from the fungus *Penicillium paxilli*, is a ligand of both LXRα and LXRβ (EC_{50} of approximately 4.0 μM for both isoforms in a luciferase reporter gene assay). It binds directly to both receptor isoforms, resulting in receptor activation and transcription of LXR target genes in cell-based assays (Bramlett et al., 2003).

Another interesting natural product is cyanidin (Table 1), an anthocyanidin found in fruits and vegetables (Manach et al., 2004). Jia et al. found that cyanidin binds to both LXRα and LXRβ, yet shows a higher affinity for LXRα than for LXRβ (EC_{50} for LXRα 3.5 μM and for LXRβ 125.2 μM). This results in the transactivation of these receptors and subsequent expression of LXR target genes like ABCA1 and ABCG5 in cell-based assays (Jia et al., 2013).

The monoterpene cineole (Table 1), a constituent of many essential oils found in teas and herbs, leads to the activation of LXRα and LXRβ, as assessed in a Gal4-responsive reporter gene assay at concentrations ranging from 50 to 200 μM. The expression of LXR target genes induced by cineole is, however, tissue-specific. In RAW264.7 macrophages, the mRNA levels of ABCA1 and ABCG1 were significantly increased by treatment with cineole. In HepG2 hepatocytes, treatment with cineole resulted in unaltered mRNA expression of SREBP-1c, whereas the mRNA expression of FAS and SCD-1 was significantly reduced. In line with these results, treatment with cineole led to a significant reduction of cholesterol levels in macrophages, yet did not induce lipogenesis in hepatocytes. The manuscript, however, contains inconsistencies since an LXRE-Luc reporter vector and LXRα/β expression plasmids for co-transfection are reported to be used in the main text, whereas the materials part and the figure legend describes the usage of a mammalian one-hybrid assay (Jun et al., 2013).

Jayasuriya et al. extracted the diterpenoid (−)-acanthoic acid (Table 1) from the roots of *Rollinia pittieri* and *Rollinia exsucca*, plants found in Costa Rica and Guyana. They showed that (–)-acanthoic acid potently and selectively activates LXRα (EC_{50} of 0.18 μM in a coactivator association assay). The authors further extracted the tetracyclic triterpenoid polycarpol (Table 1) from *Unonopsis glaucopetala* and *Minquartia guianensis*, and the polyhydroxylated sterols gorgostane-3β,9α,5α,6β,11α-tetrol and gorgost-5-ene-3β,9α,11α-triol (Table 1) from *Plexaura* species. Polycarpol and the two gorgosterols showed, similarly like (−)-acanthoic acid, selectivity for the LXRα over the LXRβ receptor. In the coactivator association assay, the EC_{50} values in regard to LXRα were 0.03 μM for polycarpol, 0.45 μM for gorgostane-3β,9α,5α,6β,11α-tetrol and 0.05 μM for gorgost-5-ene-3β,9α,11α-triol. Jayasuriya et al. isolated seven more diterpenoid, steroid and triterpenoid compounds from plant and marine sources, which were active in the coactivator association assay and/or a radioligand displacement assay, but were either not tested or not active in the mammalian one-hybrid assay and will therefore not be detailed herein. The manuscript, however, causes some confusion concerning the nomenclature and structure of the two gorgosterols. The labelling gorgostane-3β,9α,5α,6β,11α-tetrol depicts the structure of gorgost-5-ene-3β,9α,11α-triol, and the labelling gorgost-5-ene-3β,9α,11α-triol depicts a gorgostane-pentol (Jayasuriya et al., 2005).

Another compound that was found to activate LXRα is paeoniflorin (Table 1), a monoterpene glycoside from *Paeonia lactiflora* Pall. *Paeonia lactiflora* is used in Taiwanese traditional medicine for the treatment of hyperlipidemia and hyperglycemia, amongst others. The effect of paeoniflorin on LXRα was assessed in a Gal4-responsive luciferase reporter gene assay in HepG2 cells (significant effect observed at 10 μM) as well as in several luciferase reporter gene assays with different LXRα-driven promoters (Lin, 2013).

Taurine (2-aminoethanesulfonic acid; Table 1) is mainly taken up *via* the diet, but can to a small extent also be synthesized in the liver. It can be found in both human plasma and cells in millimolar concentrations (Hoang et al., 2012a; Huxtable, 1992). In the WHO-CARDIAC study, it was shown that the urinary excretion of taurine and the mortality of ischemic heart disease are inversely related (Yamori et al., 2001). Moreover, taurine reduced cholesterol contents in HepG2 cells (Yanagita et al., 2008) and increased plasma HDL levels in several *in vitro* and *in vivo* experiments (Mochizuki et al., 1998; Yokogoshi et al., 1999). Hoang et al. showed that taurine induces the transcriptional activity of LXRα, but not of LXRβ. In a LanthaScreen™ time-resolved fluorescence resonance energy transfer (TR-FRET) assay and a limited protease digestion analysis, they further showed that taurine directly interacts with the LXRα ligand binding domain (EC_{50} of 10 μM in the TR-FRET assay). Despite the activation of LXRα, taurine did not cause hepatic lipogenesis, which was suggested to be the result of an inhibition of the nuclear translocation of SREBP-1c (Hoang et al., 2012a).

The dammarane-type gynosaponin TR1 ((20*S*)-2α, 3β, 12β, 24(*S*)-pentahydroxydammar-25-ene 20-*O*-β-D-glucopyranoside; Table 1), was identified as LXRα activator (Huang et al., 2005). This saponin can be

Table 1
Natural products modulating LXRα and/or LXRβ activity.

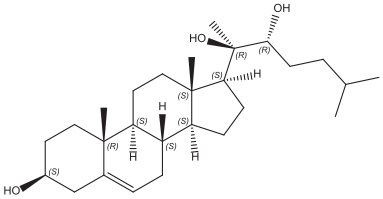
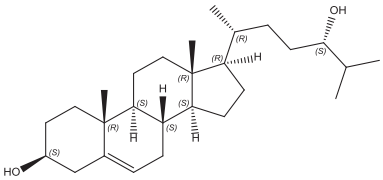
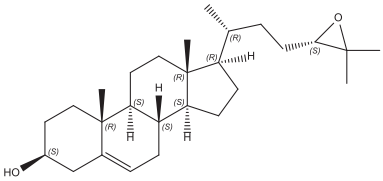
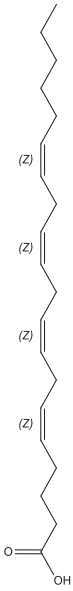
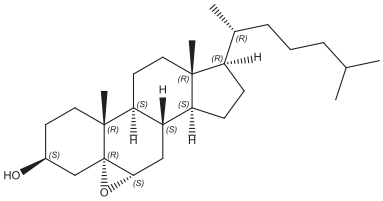
Natural product	Test system	Potency/efficacy	Reference
22(*R*)-hydroxycholesterol Endogenous agonist 	Transactivation activity in a reporter gene assay	LXRα: EC_{50} 1.5 μM (hLXRα + hRXRα, LXRE)	(Janowski et al., 1996)
		EC_{50} for LXR activation greater than 10 μM (detailed data not shown)	(Lehmann et al., 1997)
		Tested on LXRα at 10 μM (hLXRα, DR-4 reporter)	(Forman et al., 1997)
	Binding activity in a mammalian one – hybrid assay	Tested on hLXRα and hLXRβ at 10 μM	(Lehmann et al., 1997)
24(*S*)-hydroxycholesterol Endogenous agonist 	Transactivation activity in a reporter gene assay	LXRα: EC_{50} 1.6 μM (configuration at C-24 not specified; hLXRα + hRXRα, LXRE)	(Janowski et al., 1996)
		LXRα: EC_{50} 7 μM, LXRβ: EC_{50} 1.5 μM (mLXRα + CYP7A-LXRE; hLXRβ + DR-4-LXRE)	(Lehmann et al., 1997)
	Binding activity in a mammalian one – hybrid assay	Tested on hLXRα and hLXRβ at 10 μM	(Lehmann et al., 1997)
24(*S*),25-epoxycholesterol Endogenous agonist 	Binding activity in a mammalian one – hybrid assay	Tested on hLXRα and hLXRβ at 10 μM	(Lehmann et al., 1997)
	Transactivation activity in a reporter gene assay (mLXRα + CYP7A-LXRE; hLXRβ + DR4-LXRE)	LXRα: EC_{50} 7.5 μM, LXRβ: EC_{50} 1.5 μM	
Arachidonic acid Endogenous antagonist 	Binding activity in a mammalian one – hybrid assay	Tested up to 100 μM (as arachidonate) on LXRα in the presence of 24(*S*),25-epoxycholesterol	(Ou et al., 2001)
		Tested at 1–100 μM on hLXRα in the presence of 22(*R*)-hydroxycholesterol	(Yoshikawa et al., 2002)
	Coactivator interaction assay (fluorescence polarization)	Effect on the interaction between LXRα and a peptide containing the coactivator signature motif LXXLL investigated in the presence of 24(*S*),25-epoxycholesterol; IC_{50} of arachidonate 1.5 μM	(Ou et al., 2001)
	Target gene expression studies (mRNA, protein)	FTO-2B: Tested as sodium arachidonate on SREBP-1c mRNA (3–100 μM), on FAS and SCD-1 mRNA (10–100 μM) and on SREBP-1 protein (100 μM) in the presence or absence of T0901317, amongst others	
		HepG2: Tested at 50–200 μM for APOA1, ABCA1 and PLTP mRNA, amongst others	(Kuang et al., 2012)
	Transactivation activity in a reporter gene assay	Tested at 100 μM on LXRα (mSREBP-1c promoter)	(Yoshikawa et al., 2002)
		Tested at 3–100 μM on LXRα (LXRE)	
		Tested at 200 μM on LXRE, no differentiation between LXRα and LXRβ as no expression plasmids were used	(Kuang et al., 2012)
	Gel mobility shift assay	Tested at 3–30 μM for the binding of mLXRα + hRXRα proteins to LXREb in SREBP-1c promoter (in the presence or absence of T0901317)	(Yoshikawa et al., 2002)
5α,6α-epoxycholesterol Endogenous agonist, antagonist or inverse agonist (depending on setting) 	Multiplexed cofactor interaction assay	Tested at 10 μM for the recruitment of 39 cofactor peptides to LXRα- and LXRβ-LBDs	(Berrodin et al., 2010)
	Cofactor interaction assay (Alpha Screen)	LXRα: SRC-2 III recruitment EC_{50} 1.7 μM, SRC-3 III recruitment EC_{50} 1.9 μM	
		LXRβ: SRC-2 III recruitment EC_{50} 1.3 μM, SRC-3 III recruitment EC_{50} 2.8 μM	
	Competitive binding assay with [^{3}H]-T0901317 to LXRα- and LXRβ-LBDs	LXRα: IC_{50} 76 nM LXRβ: no competition observed	
	Mammalian two-hybrid assay for SRC-2 recruitment	LXRα: E_{max} 24%, EC_{50} 19 μM LXRβ: E_{max} 4%, EC_{50} 16 μM	
	Target gene expression studies (mRNA)	Tested at 10 μM for multiple LXR-responsive genes like APOE, ABCA1, ABCG1, FASN and SCD in various cell lines in the presence or absence of T0901317	

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Table 1 (*continued*)

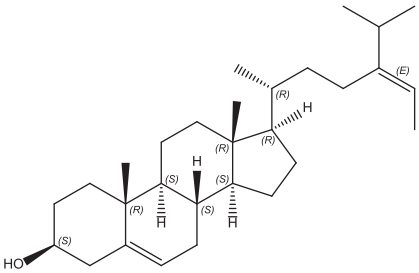
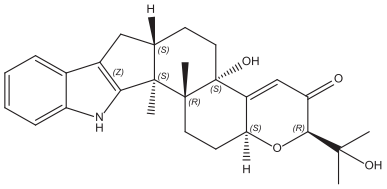
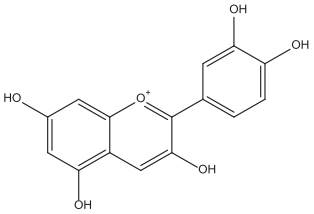
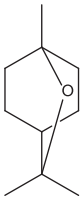
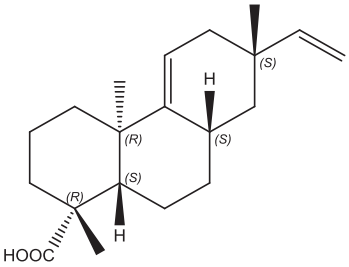
Natural product	Test system	Potency/efficacy	Reference
Fucosterol Agonist of both LXR isoforms 	Binding activity in a mammalian one – hybrid assay	Tested at 100 μM and 200 μM on hLXRα and hLXRβ	(Hoang et al., 2012b)
	Coactivator interaction assay (TR-FRET)	Tested at 0.001 μM–100 μM for TRAP220/DRIP-2 (LXRα, EC_{50} 464 nM) or D22 (LXRβ, EC_{50} 1391 nM)	
	Target gene expression studies (mRNA)	Tested at 100 μM and 200 μM for LXRα, LXRβ and multiple LXR-responsive genes in various cell lines	
	Target gene expression studies (protein)	HepG2: tested at 100 and 200 μM for precursor SREBP-1 and nuclear SREBP-1	
	Functional studies	Promotes cholesterol efflux from THP-1 derived macrophages at 100 and 200 μM Does not significantly alter cellular TG concentrations in hepatocytes at 100 and 200 μM	
Paxilline Agonist of both LXR isoforms 	Radioligand binding assay (scintillation proximity)	LXRα K_i = 660 nM, LXRβ K_i = 1100 nM	(Bramlett et al., 2003)
	Coactivator interaction assay (Alpha Screen)	Tested for recruitment of SRC-1 and TIF-2 to both LXR isoforms; LXRα: EC_{50} 1800 nM (SRC-1) and 660 nM (TIF-2); LXRβ: EC_{50} 930 nM (SRC-1) and 1200 nM (TIF-2)	
	Transactivation activity in a reporter gene assay	EC_{50} app. 4.0 μM for both LXR isoforms (hLXRα + hRXRα or LXRβ + hRXRα, LXRE derived from ABCA1 promoter) Stably transfected HepG2 with SRE reporter construct to assess the induction of SREBP: EC_{50} 2.8 μM	
	Target gene expression studies (mRNA)	Tested for ABCA1 (EC_{50} 1300 nM, THP-1) and SREBP (at 1-20 μM, HepG2)	
Cyanidin Agonist of both LXR isoforms 	Coactivator interaction assay (TR-FRET)	Tested for TRAP220/DRIP-2 (hLXRα, EC_{50} 3.5 μM) and D22 (hLXRβ, EC_{50} 125.2 μM)	(Jia et al., 2013)
	Transactivation activity in a reporter gene assay (LXRα or LXRβ, LXRE)	Tested at 5–100 μM	
	Surface Plasmon Resonance with hLXR-LBDs	LXRα K_D = 2.2 μM, LXRβ K_D = 73.2 μM	
	Target gene expression studies (mRNA)	HepG2: Tested at 1–100 μM for LXRα, LXRβ, ABCA1, ABCG5 and SREBP-1c	
	Functional studies	Cyanidin reduces cellular lipid concentrations in THP-1 cells and lipid-loaded HepG2 cells	
Cineole Agonist of both LXR isoforms 	Binding activity in a mammalian one – hybrid assay	Tested at 50–200 μM on hLXRα and hLXRβ	(Jun et al., 2013)
	Coactivator interaction assay (TR-FRET)	Tested at 0.0001 nM–1 mM for TRAP220/DRIP-2 (LXRα) and D22 (LXRβ)	
	Target gene expression studies (mRNA)	Tested at 50 μM and 100 μM for LXRα, LXRβ, ABCA1 and ABCG1 (RAW264.7) and for LXRα, FAS, SCD-1 and SREBP-1c (HepG2)	
	Target gene expression studies (protein)	Tested at 50 μM and 100 μM for LXRα, LXRβ and ABCA1 (RAW264.7) and for LXRα, FAS and SREBP-1c (HepG2)	
	Functional studies	Cineole reduces cellular cholesterol levels in RAW264.7 cells and reduces lipid accumulation in HepG2 cells	
(−)-Acanthoic acid Agonist of LXRα 	Coactivator association assay (homogeneous time-resolved fluorescence)	Tested for recruitment of SRC-1 to both LXR-LBDs; LXRα: EC_{50} 0.18 μM, no association with LXRβ-LBD at 50 μM	(Jayasuriya et al., 2005)
	Radioligand displacement assay (scintillation proximity)	LXRα: IC_{50} 0.25 μM, LXRβ: IC_{50} 1.49 μM	
	Binding activity in a mammalian one – hybrid assay	Tested up to 100 μM on LXRα and LXRβ	
Polycarpol Agonist of LXRα	Coactivator association assay (homogeneous time-resolved fluorescence)	Tested for recruitment of SRC-1 to both LXR-LBDs; LXRα: EC_{50} 0.03 μM, no association with LXRβ-LBD at 50 μM	(Jayasuriya et al., 2005)
	Radioligand displacement assay (scintillation proximity)	LXRα: IC_{50} 0.12 μM, LXRβ: IC_{50} > 15 μM	
	Binding activity in a mammalian one-hybrid assay	At 2.2 μM 8-fold induction of LXRα, not tested on LXRβ	

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Table 1 (*continued*)

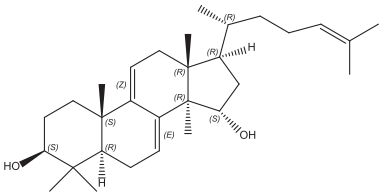
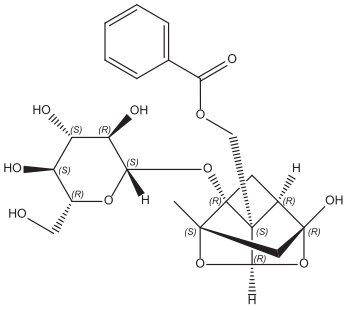
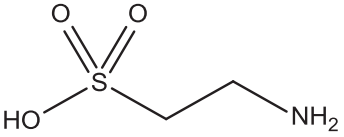
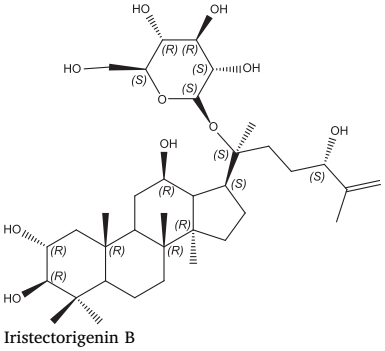
Natural product	Test system	Potency/efficacy	Reference
			
Gorgostane-3β,9α,5α,6β,11α-tetrol Agonist of LXRα	Coactivator association assay (homogeneous time-resolved fluorescence)	Tested for recruitment of SRC-1 to LXRα-LBD; LXRα: EC_{50} 0.45 μM	(Jayasuriya et al., 2005)
Due to inconclusiveness regarding the structure, no structure depicted (see text)	Radioligand displacement assay (scintillation proximity)	LXRα: IC_{50} 1.3 μM, LXRβ: IC_{50} 50 μM	
	Binding activity in a mammalian one-hybrid assay	At 30 μM 10.1-fold induction of LXRα, no activity detected for LXRβ at 30 μM	
Gorgost-5-ene-3β,9α,11α-triol Agonist of LXRα	Coactivator association assay (homogeneous time-resolved fluorescence)	Tested for recruitment of SRC-1 to both LXR-LBDs; LXRα: EC_{50} 0.05 μM, no association with LXRβ-LBD at 10 μM	(Jayasuriya et al., 2005)
Due to inconclusiveness regarding the structure, no structure depicted (see text)	Radioligand displacement assay (scintillation proximity)	LXRα: IC_{50} 0.07 μM, LXRβ: IC_{50} 0.2 μM	
	Binding activity in a mammalian one-hybrid assay	At 10 μM 13-fold induction of LXRα and 2.2-fold induction of LXRβ	
Paeoniflorin Agonist of LXRα (only tested for LXRα activation)	Binding activity in a mammalian one – hybrid assay	Tested at 0.1–100 μM on hLXRα; EC_{50} 8.7 μM	(Lin, 2013)
	Transactivation activity in a reporter gene assay (hLXRα + hRXRα)	Tested at 0.1–100 μM EC_{50} (PLTP promoter) 21.6 μM, EC_{50} (ABCA1 promoter) 11.9 μM, EC_{50} (rat CYP7A1 promoter) 66 μM	
Taurine Agonist of LXRα	Coactivator interaction assay (TR-FRET)	Tested for recruitment of TRAP220/DRIP-2 to LXRα, EC_{50} 10 μM	(Hoang et al., 2012a)
	Limited protease digestion analysis	hLXRα-LBD was preincubated with 100 μM taurine and then subjected to digestion with protease K	
	Transactivation activity in a reporter gene assay (hLXRα or hLXRβ, LXRE)	Tested at 10, 50 and 100 μM	
	Target gene expression studies (mRNA)	Tested at 10, 50 and 100 μM for LXRα and multiple LXR-responsive genes in THP-1, HepG2, H4IIE and Caco-2 cells	
	Target gene expression studies (protein)	THP-1: LXRα, ABCA1, ABCG1 HepG2: pSREBP-1, nSREBP-1, amongst others	
	Functional studies	Taurine reduces cellular cholesterol levels in both THP-1 derived macrophages and HepG2 cells and decreases TG concentrations in HepG2	
TR1 Agonist of LXRα	Transactivation activity in a reporter gene assay (hLXRα or hLXRβ, LXRE)	Tested at 0.1–10 μM	(Huang et al., 2005)
	Target gene expression studies (mRNA)	THP-1: Tested at 1 and 10 μM for LXRα, ABCA1 and APOE	
	Target gene expression studies (protein)	THP-1: Tested at 1 and 10 μM for LXRα and ABCA1; tested at 0.1, 1 and 10 μM for APOE protein secretion	
Iristectorigenin B Agonist of both LXR isoforms	Binding activity in a mammalian one – hybrid assay	Tested at 5–20 μM on hLXRα and hLXRβ	(Jun et al., 2012)
	Target gene expression studies (mRNA)		

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Table 1 (*continued*)

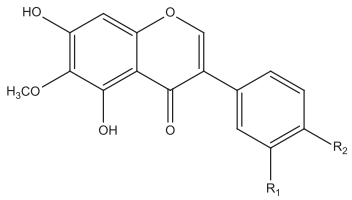
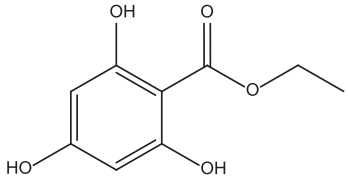
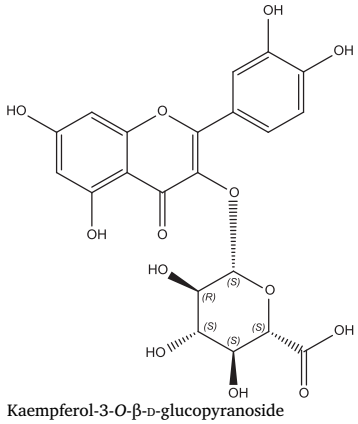
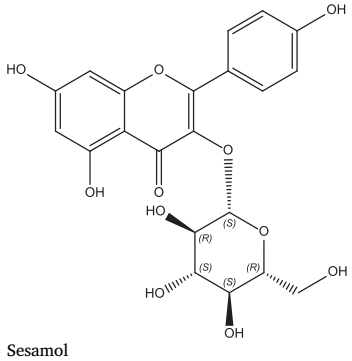
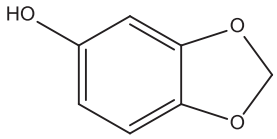
Natural product	Test system	Potency/efficacy	Reference
 iristectorigenin A: R_1 = OCH_3, R_2 = OH iristectorigenin B: R_1 = OH, R_2 = OCH_3	Functional studies	Tested at 5 and 10 μM for ABCA1 and ABCG1 (RAW264.7) and SREBP-1c, FAS and SCD-1 (HepG2) Iristectorigenin B increases cholesterol efflux and reduces cellular cholesterol levels in RAW264.7; it does not increase TG levels in HepG2	
ETB Agonist of both LXR isoforms 	Binding activity in a mammalian one – hybrid assay Coactivator interaction assay (TR-FRET) Surface Plasmon Resonance with LXR-LBDs Target gene expression studies (mRNA) Target gene expression studies (protein) Functional studies	Tested at 50 and 100 μM on hLXRα and hLXRβ LXRα EC_{50} 80.76 μM, LXRβ EC_{50} 37.8 Tested for recruitment of TRAP220/DRIP-2 (LXRα, EC_{50} 1.50 μM) and D22 (LXRβ, EC_{50} 3.04 μM) Tested at 100 μM Tested at 50 and 100 μM for ABCA1, ABCG1 and several other LXR-responsive genes in THP-1, RAW264.7, Caco-2 and HepG2 THP-1: ABCA1, ABCG1 HepG2: pSREBP-1, nSREBP-1 ETB increases cholesterol efflux and reduces cellular cholesterol levels in THP-1 cells; it reduces cholesterol levels in RAW264.7, Caco-2 and HepG2; it does not increase TG levels in HepG2	(Hoang et al., 2012c)
Quercetin-3-*O*-glucuronide Agonist of LXRα (only tested on LXRα) 	Coactivator interaction assay (receptor cofactor assay system) Target gene expression studies (mRNA, protein)	Tested at 50 μM for the influence on the affinity between LXRα and a peptide containing the LXXLL motif of SRC-1 RAW264.7: Tested at 50 μM for ABCA1	(Ohara et al., 2013)
Kaempferol-3-*O*-β-D-glucopyranoside Agonist of LXR (no differentiation between LXRα and LXRβ) 	Transactivation activity in a reporter gene assay (LXR, LXRE)	EC_{50} 1.8 μM	(He et al., 2012)
Sesamol Agonist of LXR (no differentiation between LXRα and LXRβ possible) 	Transactivation activity in a reporter gene assay (no LXRα or LXRβ expression plasmid used, LXRE) Luciferase reporter assay for evaluation of LXRα expression Functional studies	Tested at 25–100 μM Tested at 25–100 μM on mLXRα-Luc Tested at 25–100 μM on cholesterol efflux from mouse peritoneal macrophages	(Majdalawieh and Ro, 2015)

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Table 1 (*continued*)

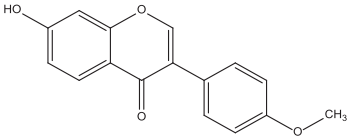
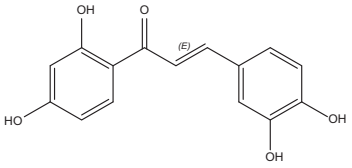
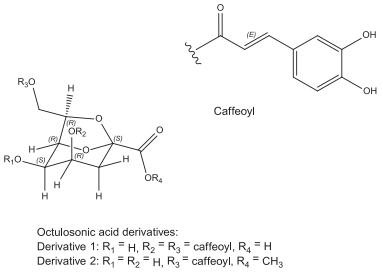
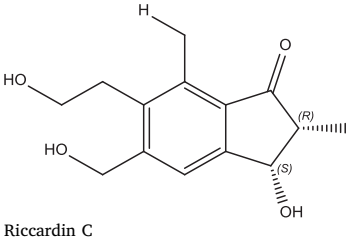
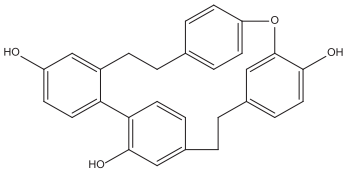
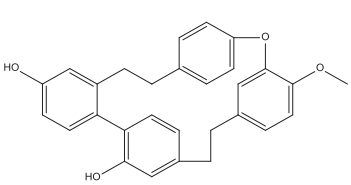
Natural product	Test system	Potency/efficacy	Reference
Formononetin Agonist of LXR (no differentiation between LXRα and LXRβ) 	Transactivation activity in a reporter gene assay (no LXRα or LXRβ expression plasmid used)	Tested at 1–10 μM on LXRE (derived from hABCA1 promoter) and at 2–10 μM on ABCA1	(Iio et al., 2012)
Butein Data indicative of LXR agonism	Transactivation activity in a reporter gene assay	Tested at 1 μg/ml (no expression plasmid used, a 3.2 kb portion of the mouse CYP7A1 promoter used)	(Jeong et al., 2015)
	Transactivation activity in a reporter gene assay	Repetition of the assay after LXRα knockdown: knockdown of LXRα significantly reduced the activation of the CYP7A1 promoter; no concentrations given	
Octulosonic acid derivatives Agonists of LXRα (only tested for LXRα activation)  Caffeoyl Octulosonic acid derivatives: Derivative 1: R_1 = H, R_2 = R_3 = caffeoyl, R_4 = H Derivative 2: R_1 = R_2 = H, R_3 = caffeoyl, R_4 = CH_3	Transactivation activity in a reporter gene assay (hLXRα, LXRE)	Tested at 30 μM	(Zhao et al., 2014a, 2014b)
(2*R*,3*S*)-5-hydroxymethylpterosin C Agonist of LXRα and LXRβ 	Transactivation activity in a reporter gene assay (hLXRα or hLXRβ + hRXRα, LXRE) Functional studies	Tested at 10 μM Reduces TG levels in 3T3-L1 cells significantly from 1.1 μM onwards	(Luo et al., 2016)
Riccardin C Partial agonist of LXRα and antagonist of LXRβ 	Transactivation activity in a reporter gene assay (LXRα or LXRβ + RXRα, LXRE) Coactivator association assay (fluorescence polarization) Target gene expression studies (mRNA)	Tested at various concentrations on both LXR isoforms, concentrations not given Performed also in the presence of full agonist (RC 10 or 30 μM + various concentrations of T0901317) Tested at 1–10 μM for recruitment of SRC-1 to hLXRα and hLXRβ Performed in the presence and absence of full agonist (T0901317) Tested at 30 μM for ABCA1 (THP1) and ABCG1 (THP1, HepG2), tested at 30 μM for SREBP-1c in the presence or absence of a full agonist (THP-1, HepG2)	(Tamehiro et al., 2005)
Riccardin F Antagonist of LXRα 	Transactivation activity in a reporter gene assay (LXRα or LXRβ + RXRα, LXRE) Coactivator association assay (fluorescence polarization) Target gene expression studies	Tested at various concentrations on both LXR isoforms, concentrations not given Performed also in the presence of full agonist (RF 10 or 30 μM + various concentrations of T0901317) Tested at 1–10 μM for recruitment of SRC-1 to hLXRα and hLXRβ Performed in the presence and absence of full agonist (T0901317) THP-1, HepG2: Tested at 30 μM for SREBP-1c in the presence or absence of a full agonist	(Tamehiro et al., 2005)
Rhein Data indicative of LXR antagonism	Binding activity in a mammalian one – hybrid assay Target gene expression studies (mRNA)	Tested at 6.25–50 μM in the presence of GW3965 1 μM for both LXR isoforms Tested at 25 μM for SREBP-1c, FAS, SCD-1 and ACC in the presence of GW3965 1 μM	(Sheng et al., 2011)

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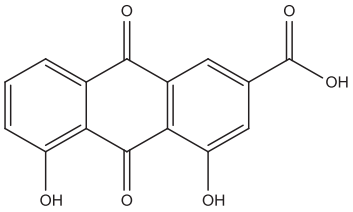
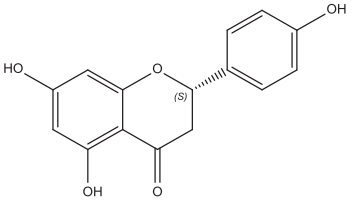
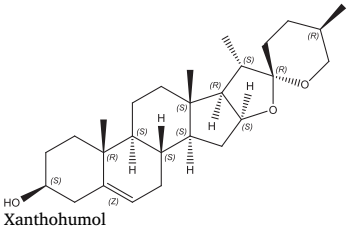
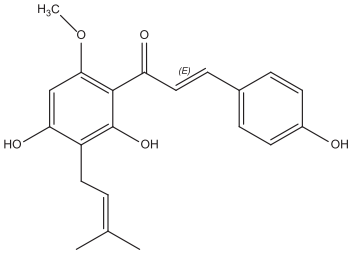
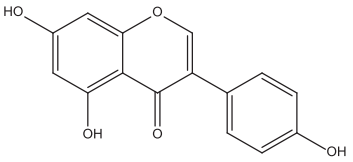
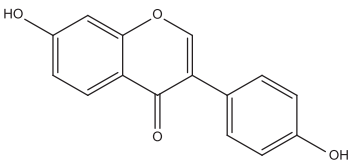
Table 1 (*continued*)

Natural product	Test system	Potency/efficacy	Reference
	Mouse model of diet induced obesity	Investigation of hepatic gene expression of SREBP-1c, FAS and SCD-1 amongst others, after treatment with rhein (150 mg/kg)	
	LXRα/β knockout	Rhein reduces body weight and fat weight, improves serum lipids and glucose metabolism, decreases liver lipids and reverses hepatic steatosis	Investigation of hepatic gene expression of SREBP-1c, FAS and SCD-1 amongst others, after treatment with rhein (150 mg/kg)
($LXR^{-/-}$) and WT mice on a high fat diet			
Naringenin Modulator of LXRα activity (only tested on LXRα)	Binding activity in a mammalian one – hybrid assay (LXR-alpha-UAS-bla HEK293T cells)	Tested at 0.4–400 μM in the presence of 4.7 nM T0901317	(Goldwasser et al., 2010)
	Coactivator interaction assay (TR-FRET)	Tested for recruitment of TRAP220/DRIP-2 to LXRα-LBD in the presence or absence of T0901317	
	Transactivation activity in a reporter gene assay (no expression plasmids used, LXRE)	Tested at 50–200 μM	
	Target gene expression studies (mRNA)	Tested at 200 μM for LXRα, ABCA1, ABCG1, HMGR and FASN	
Diosgenin Data indicative of LXRα antagonism (only tested on LXRα)	Binding activity in a mammalian one – hybrid assay	Tested at 1–10 μM on hLXRα in the presence of T0901317	(Uemura et al., 2011)
	Gel mobility shift assay	Tested at 1–10 μM in the presence of T0901317	
	Target gene expression studies (mRNA)	HepG2: Tested at 10 μM on FAS, SCD-1, ACC and SREBP-1c; tested at 1–10 μM on FAS, SCD-1, ACC and SREBP-1c in the presence of T0901317	
	Target gene expression studies (protein)	HepG2: precursor SREBP-1 and mature SREBP-1 in the presence and absence of T0901317	
	Functional studies	HepG2: TG levels reduced	
Xanthohumol Data indicative of LXR antagonism	Target gene expression studies	HepG2: Tested at 10 and 20 μM on Mylip/Idol (mRNA, protein) and nuclear LXRα (protein); pretreatment with 20 μM followed by treatment with T0901317 and then tested on Mylip/Idol (mRNA, protein)	(Chen et al., 2017)
			
Genistein Data indicative of indirect modulation of LXRs	Transactivation activity in a reporter gene assay (LXRα or LXRβ, LXRE)	Tested at 0.1–10 μM in the presence or absence of full agonists (GW3965, 22(*R*)-hydroxycholesterol) → no activity detected	(Gonzalez-Granillo et al., 2012)
	Gene expression analysis (mRNA)	Tested at 15 μM on ABCA1, ABCG5, ABCG8 and SREBP-1c in LXRα or LXRβ overexpressing mouse hepatocytes in the presence or absence of T0901317	
Daidzein Data indicative of indirect modulation of LXRs	Transactivation activity in a reporter gene assay (LXRα or LXRβ, LXRE)	Tested at 0.5–20 μM in the presence or absence of full agonists (GW3965, 22(*R*)-hydroxycholesterol) → no activity detected	(Gonzalez-Granillo et al., 2012)
	Gene expression analysis (mRNA)	Tested at 15 μM on ABCA1, ABCG5, ABCG8 and SREBP-1c in LXRα or LXRβ overexpressing mouse hepatocytes in the presence or absence of T0901317	

found in *Gynostemma pentaphyllum*, which is a vine endemic in China, Japan, India and Korea, and which is used as a Chinese herbal medicine (Huang et al., 2005). Studies have indicated that *G. pentaphyllum* has anti-inflammatory as well as antioxidant activities, amongst others (Li et al., 1993; Lin et al., 1993). In a luciferase reporter gene assay in HEK293 cells, Huang et al. showed that TR1 significantly activated LXRα at 10 μM, while it did not significantly affect LXRβ activity. Furthermore, TR1 treatment led to an increase in both mRNA and protein levels of ABCA1, as well as to an increase in APOE mRNA expression and APOE secretion in THP-1-derived macrophages (Huang et al., 2005).

A shrub endemic to East Asia, *Belamcanda chinensis*, is used in Asian

traditional medicine to treat inflammation and asthma. Jun et al. showed in a Gal4-responsive luciferase reporter gene assay that the *Belamcanda* constituent, iristectorigenin B (Table 1), significantly activates both LXRα and LXRβ already at 10 μM. Iristectorigenin B further increased ABCA1 and ABCG1 mRNA levels in RAW264.7 macrophages and significantly enhanced cholesterol efflux from these cells. Interestingly, it did not induce the expression of the lipogenic genes SREBP-1c, FAS and SCD-1, and did not lead to triacylglycerol accumulation in HepG2 cells. Notably, the structure depicted by the authors is iristectorigenin A, whereas in the text, they always address iristectorigenin B (Jun et al., 2012).

Hoang et al. isolated ethyl 2,4,6-trihydroxybenzoate (ETB; Table 1) from *Celtis biondii* and tested it regarding its ability to activate nuclear receptors. In a Gal4-responsive reporter gene assay in HEK293 cells, it was shown that ETB significantly activated both LXRα and LXRβ at 100 μM and 50 μM, respectively. By means of TR-FRET and surface plasmon resonance (SPR) analysis it was assessed that ETB directly binds to both LXR isoforms and recruits the coactivators Trap 220/Drip-2 to the ligand binding domain (LBD) of LXRα and D22 to the LBD of LXRβ. Moreover, ETB increased cholesterol efflux from THP-1-derived macrophages and reduced cellular cholesterol levels in macrophages, hepatocytes and intestinal cells. Remarkably, ETB did not cause accumulation of triglycerides in hepatocytes (Hoang et al., 2012c).

The widely distributed flavonoid, quercetin, exerts antioxidant, anti-inflammatory and antiatherogenic activity (Hayek et al., 1997; Lee et al., 2013). Lee et al. showed that quercetin (0.3 μM) leads to a significant upregulation of ABCA1 mRNA and protein levels in THP-1 macrophages. Moreover, quercetin increased cholesterol efflux from THP-1 macrophages and led to elevated protein levels of PPARγ and LXRα (Lee et al., 2013). When quercetin or quercetin glycosides are absorbed from the gastrointestinal tract, they rapidly undergo metabolism, resulting in the formation of quercetin-3-*O*-glucuronide (Q3GA; Table 1), amongst others (Moon et al., 2001; Sesink et al., 2001). Ohara et al. showed in their study that Q3GA (50 μM) increases ABCA1 mRNA and protein levels in RAW264.7 macrophages. They further investigated a potential role of LXRα in this effect by means of a receptor coactivator recruitment assay. Both Q3GA and the quercetin aglycon significantly increased the recruitment of SRC-1 to LXRα indicating that they are LXRα ligands (Ohara et al., 2013).

Kaempferol-3-*O*-β-D-glucopyranoside (Table 1) is a flavonoid that is widely distributed and can be found in plants like *Cornus alternifolia*, as well as in food plants like black beans (*Phaseolus vulgaris*) (Dong et al., 2007; He et al., 2012). *Via* luciferase reporter gene assays in HepG2 cells or CHO cells, it has been shown that Kaempferol-3-*O*-β-D-glucopyranoside is a potent agonist of PPARα, PPARγ and LXR with EC_{50} values of 0.62 μM, 3.0 μM and 1.8 μM, respectively (He et al., 2012).

Sesame oil, obtained from the seeds of sesame, *Sesamum indicum*, has beneficial effects on lipid metabolism and modulates inflammation. It has been shown to reduce total cholesterol and LDL cholesterol levels in serum of hyperlipidemic rats (Periasamy et al., 2013; Satchithanandam et al., 1996). In a luciferase reporter gene assay in CHO cells, sesame oil and a lignan found in sesame oil, sesamol (Table 1), significantly activated LXR at 5 μg/ml and 50 μM, respectively. (Majdalawieh and Ro, 2015). Selvarajan et al. showed that an aqueous extract of sesame oil (SOAE, 100 μg/ml) could significantly increase luciferase activity in a HepG2-LXR reporter cell line, indicating LXR activation by SOAE (Selvarajan et al., 2015).

A very popular substance used in folk medicine is propolis, which is collected by honey bees from different plants. In the northeast of Brazil, a new type of propolis was found, called red propolis, which is derived from *Dalbergia ecastophyllum* (L) Taub. Components found in red propolis include isoflavonoids, triterpenoids and prenylated benzophenons (Daugsch et al., 2008; Silva et al., 2008; Trusheva et al., 2006). Iio et al. evaluated the effect of ethanolic extracts of Brazilian red propolis (EERP) on the transcriptional activity of LXR and PPARγ in luciferase reporter gene assays in THP-1 macrophages. EERP dose-dependently (5–15 μg/ml) activated both LXR and PPARγ and led to an upregulation of ABCA1 mRNA and protein levels (Iio et al., 2012). One of the major isoflavones found in Brazilian red propolis is formononetin (Table 1) (Daugsch et al., 2008). Formononetin enhanced LXR activity already at a concentration of 1 μM in the same assay (Iio et al., 2012).

A plant that was traditionally used as herbal medicine in South Korea is *Rhus verniciflua* Stokes (RVS) (Oh et al., 2006). Jeong et al. investigated an extract of RVS in a luciferase reporter gene assay in the mouse hepatocyte cell line AML 12, using a reporter plasmid containing a 3.2-kb portion of the mouse CYP7A1 promoter. They found that the RVS extract (10 μg/ml) significantly increased luciferase activity, which indicated an activation of the CYP7A1 promoter. Subsequently, they evaluated eight single compounds and detected increased luciferase activity after treatment with sulfuretin, butein (Table 1) or quercetin (each at 1 μg/ml), with butein being most effective. To investigate whether the increase in luciferase activity caused by butein was LXRα-dependent, LXRα was knocked down by siRNA. Knockdown of LXRα resulted in a significant reduction of butein-induced luciferase activity, suggesting that LXRα is essential for the activation of the CYP7A1 promoter caused by butein (Jeong et al., 2015).

Roman chamomile, *Chamaemelum nobile* (L.) All., is a plant endemic in southern Europe, which is used traditionally to treat nausea, dyspepsia and wounds, for example. Several studies have revealed anti-inflammatory, hypoglycemic and antioxidant properties of Roman chamomile. Zhao et al. isolated six new compounds from the flower heads of *Chamaemelum nobile*, all of them being octulosonic acid derivatives. Two of these compounds (Table 1) were shown to activate LXRα at a concentration of 30 μM in a luciferase reporter gene assay in HepG2 cells (Zhao et al., 2014a).

A plant found e.g. in the south and southwest of China, which is also used in traditional Chinese medicine, is *Pteris cretica* L. Luo et al. isolated several new and already known compounds from the aerial parts of this plant. Among them was one new pterosin sesquiterpenoid ((2*R*,3*S*)-5-hydroxymethylpterosin C; Table 1) that activated both LXRα and LXRβ at 10 μM in a luciferase reporter gene assay. Amazingly, the activation of both LXR isoforms induced by this compound was more pronounced than with GW3965 (10 μM) (Luo et al., 2016).

The non-steroidal natural products riccardin C (RC, Table 1) and riccardin F (RF, Table 1), which can be found in the liverwort *Blasia pusilla*, also interact with LXRα and LXRβ. It was shown that riccardin C is a partial agonist of LXRα (approximately 15-fold increase in luciferase activity at 30 μM in CV-1 cells) and an antagonist of LXRβ, whereas riccardin F is an antagonist of LXRα. Despite its antagonistic activity on LXRβ, riccardin C was able to significantly enhance cholesterol efflux from THP-1 macrophages (Tamehiro et al., 2005).

Rheum palmatum L. is used in traditional Chinese medicine for the treatment of gastrointestinal ulcers and obstipation. A major anthraquinone found in *Rheum palmatum* L. is rhein (Table 1) (Huang et al., 2007). In a Gal4-responsive luciferase reporter gene assay, rhein concentration-dependently (from 6.25 μM to 50 μM) reduced GW3965-mediated activation of both LXRα and LXRβ. Moreover, rhein decreased mRNA expression of SREBP-1c and its target genes FAS, SCD-1 and ACC2, which were increased upon GW3965 treatment. These data are indicative of LXR antagonism by rhein. However, if rhein really acts as LXR antagonist has to be verified in a direct binding assay (Sheng et al., 2011).

Naringenin (Table 1) is a flavonoid aglycone found e.g. in grapefruits. The naringenin glycoside, naringin, reduced both total cholesterol and LDL levels in a clinical trial and further lowered cholesterol and triglyceride levels in rats (Jung et al., 2003; Kim et al., 2006b). In hepatocytes, naringenin decreased the secretion of APOB and caused an upregulation of enzymes involved in hepatic fatty acid oxidation (Borradaile et al., 1999; Huong et al., 2006). In a Gal4-responsive beta-lactamase reporter gene assay, naringenin concentration-dependently ($p < 0.01$ at 126 μM) reduced LXRα activation induced by T0901317. The authors of this study further investigated naringenin in a

LanthaScreen™ TR-FRET assay, where they found that it weakly, but significantly, increased the binding of the LXRα LBD to the coactivator peptide Trap 220/Drip-2, whereas it dose-dependently inhibited this binding when co-administered with T0901317. These results led the authors to the assumption that naringenin might be a partial agonist of LXRα. However, in a luciferase reporter gene assay performed in a human liver cell line, naringenin dose-dependently inhibited the activation of LXR (Goldwasser et al., 2010).

Diosgenin (Table 1) is a hydrolyzed saponin, which can be found in fenugreek (*Trigonella foenum-graecum*), amongst others. Uemura et al. showed that diosgenin (1–10 μM) inhibits T0901317-activated LXRα in a Gal4-responsive reporter gene assay. Furthermore, diosgenin decreases mRNA levels of SREBP-1c, FAS, SCD-1 and ACC, both in the presence and absence of T0901317. Likewise, in the presence or absence of T0901317, diosgenin dose-dependently reduced triglyceride accumulation in HepG2 cells (Uemura et al., 2011).

A prenylated flavonoid found in hops (*Humulus lupulus* L.) is xanthohumol (Table 1). Xanthohumol has various biological activities, ranging from anti-inflammatory to neuroprotective and anti-angiogenic effects (Costa et al., 2013; Yen et al., 2012). In a mouse model of obesity and type 2 diabetes (KK-A^y mice), xanthohumol was capable of improving glucose and lipid metabolism (Nozawa, 2005). In the CETP-transgenic mouse model, it even decreased cholesterol accumulation in the aortic arch and raised HDL levels (Hirata et al., 2012). In the study of Chen et al., xanthohumol increased LDL uptake in HepG2 cells and elevated LDL receptor (LDLR) on the cell surface. The increase in LDLR on the cell surface was associated with an increase in LDLR protein level, but not with an increase in mRNA levels. Since LDLR degradation is enhanced by inducible degrader of the LDL receptor (Mylip/Idol), the authors investigated the expression of this protein. Treatment with xanthohumol (10 and 20 μM) significantly decreased the expression of Mylip/Idol mRNA and protein, which might be responsible for the increase in LDLR levels in HepG2 cells. As Mylip/Idol is a direct target gene of LXR, Chen et al. investigated the implication of LXR in the reduction of Mylip/Idol expression. For that purpose, they pretreated the cells with 20 μM xanthohumol followed by incubation with T0901317. Under these conditions, both mRNA and protein levels of Mylip/Idol were reduced compared to the T0901317 single treatment. Since the mRNA and protein levels of LXRα were not changed, they assumed that xanthohumol counteracts LXR activation. To support this hypothesis, they performed molecular docking, where they showed that xanthohumol docked into the LXRα LBD in a similar pose as T0901317 does (Chen et al., 2017).

An ethanolic extract of *Ilex kudingcha* C. J. Tseng, also known as kuding tea, was shown to exert antagonistic activity on LXRβ in a Gal4-responsive luciferase reporter gene assay (5 μg/ml against GW3965). In traditional Chinese medicine, kuding tea has been used for over 2000 years to treat metabolic diseases like obesity, hyperlipidemia or cardiovascular disease. In mice on a high-fat diet, the ethanolic extract showed both preventive and therapeutic effects in regard to metabolic disorders. Concomitant administration of a high-fat diet and of the ethanol extract of kuding tea resulted in less weight gain, reduced serum total cholesterol, as well as improved glucose tolerance and reduced lipid accumulation in the liver compared to untreated mice. Already obese mice that were administered the ethanolic extract showed lower serum triglyceride and fasting glucose levels in comparison to control mice. The positive effect of the ethanolic kuding tea extract on metabolic disorders is likely based on multiple mechanisms and LXRβ antagonism may be part of it as suggested by the study of Fan et al. (Fan et al., 2012).

Two whole leaf methanol extracts from *Parthenocissua tricuspidata* (MEH184) and *Euscaphis japonica* (MEH185) were shown to decrease LXRα activation dose-dependently (tested at 10 μg/ml and 50 μg/ml) in a cell-based reporter gene assay, whereas they were inactive on LXRβ. Moreover, the two extracts reduced the expression of the LXR target genes FAS and SREBP-1c in hepatoma cells as well as in adipocytes (Kim et al., 2006a).

The white button mushroom (WBM), *Agaricus bisporus*, was shown to exert protective effects against hepatic steatosis in ovariectomized mice, which were used as a model of postmenopausal women. The authors of the corresponding study showed that mice receiving a high-fat diet containing white button mushroom powder (120 g/kg diet) had less fat accumulation in the liver compared to the control group. Furthermore, liver tissues of white button mushroom-fed mice displayed reduced mRNA levels of FAS and fatty acid elongase 6 (Elovl6). Similarly, FAS, ELOVL6 and SREBP-1c gene expression were decreased in HepG2 cells treated with WBM extract (1 and 5 μl/ml). In a luciferase reporter gene assay performed in HepG2 cells, treatment with the WBM extract resulted in a significant decrease of LXRα activation mediated by T0901317. Treatment with the WBM extract alone resulted in a slight, yet not significant, increase in LXRα activity (Kanaya et al., 2011).

The traditional medicinal herb *Cyperus rotundus*, also known as purple nutsedge, possesses anti-inflammatory (Seo et al., 2001), antidiabetic (Raut and Gaikwad, 2006) as well as anti-obesity activity (Lemaure et al., 2007). Oh et al. extracted the rhizome of *Cyperus rotundus* and prepared six fractions *via* sequential partitioning. They performed luciferase reporter gene assays in HepG2 cells with luciferase reporters either containing synthetic LXRE, natural SREBP-1c LXRE or natural ABCA1 LXRE. Interestingly, the hexane fraction (CRHF, 100 μg/ml) inhibited the LXR-dependent activation of the synthetic LXRE promoter and the SREBP-1c promoter induced by T0901317. In contrast, the T0901317-induced activation of the ABCA1 promoter was not inhibited by CRHF. In mouse primary hepatocytes, these results were also reflected on the mRNA level – the expression of SREBP-1c induced by T0901317 was inhibited by CRHF, while the expression of ABCA1 induced by T0901317 remained unaffected. These results suggest that CRHF might selectively inhibit lipogenesis, without affecting reverse cholesterol transport (Oh et al., 2015).

Several meta-analyses showed that the intake of soy protein is able to reduce both total and LDL cholesterol (Anderson et al., 1995; Zhan and Ho, 2005). Animal studies have further shown that soy protein leads to a reduction of liver cholesterol and triacylglycerol (Torre-Villalvazo et al., 2008; Tovar et al., 2005) and enhances the sensitivity for insulin (Noriega-Lopez et al., 2007). In a luciferase reporter gene assay in HepG2 cells, two soy isoflavones, genistein and daidzein (Table 1), were not able to activate any of the LXR isoforms. According to these data, neither genistein nor daidzein exert their effect *via* direct LXR agonism. In LXRα-overexpressing hepatocytes, co-treatment with T0901317 and genistein (15 μM) reduced SREPB-1c mRNA expression significantly compared to treatment with T0901317 alone. This effect was not found in hepatocytes overexpressing LXRβ. The opposite was observed for ABCG8 mRNA expression: co-treatment of hepatocytes overexpressing LXRα with T0901317 and genistein did not cause any significant changes compared to T0901317 treatment alone. In LXRβ overexpressing hepatocytes, co-treatment with T0901317 and genistein caused a significant increase in ABCG8 mRNA in comparison to T0901317 treatment only. These data suggest that isoflavones reduce SREBP-1c expression *via* LXRα, whereas they increase ABCG8 expression *via* LXRβ. However, the modulation of LXR activity seems to occur indirectly (Gonzalez-Granillo et al., 2012) and possibly *via* AMP-activated protein kinase (AMPK), since LXRα activity can be modulated by phosphorylation (Gonzalez-Granillo et al., 2012; Hwahng et al., 2009; Torra et al., 2008).

Abelmoschus esculentus L. Moench, also known as Okra, is a vegetable endemic in Africa which reduces the risk of cataract and glaucoma in patients with type 2 diabetes upon regular intake (Fan et al., 2013; Moise et al., 2012). Major constituents of Okra include polysaccharides and polyphenols (Arapitsas, 2008; Lengsfeld et al., 2004). In rats with streptozotocin-induced diabetes, it has been shown that peel and seed powders of *A. esculentus* exert antidiabetic and antihyperlipidemic effects (Sabitha et al., 2011). Fan et al. showed in their study in high-fat

diet-induced obese C57BL/6 mice, that treatment with okra polysaccharides (high-fat diet mixed with 1% okra polysaccharides) decreases the levels of total, HDL and LDL cholesterol. The authors further investigated the effects of okra polysaccharides on the mRNA levels of LXRα/β target genes in the livers of these mice. They showed that treatment with okra polysaccharides reduces the expression levels of ABCG1, APOE, CYP7A1 and LPL, which led them to suggest that okra polysaccharides might inhibit LXR signaling (Fan et al., 2013).

2.4. LXR as target in precision medicine

Several studies have been conducted to identify single nucleotide polymorphisms (SNPs) in the genes encoding LXRα (NR1H3) and LXRβ (NR1H2). Several SNPs have been found in both NR1H3 and NR1H2, some of them having an influence on metabolic diseases like type 2 diabetes or coronary heart disease.

Highly investigated is the SNP rs12221497 (c.-115G > A) in the LXRα gene. Robitaille et al. showed that levels of total plasma cholesterol were higher in French-Canadian individuals carrying the -115A allele compared to -115GG homozygotes when placed on a cholesterol-rich diet. Moreover, they also found a correlation between dietary cholesterol intake and LDL cholesterol levels in individuals with this polymorphism. In contrast, cholesterol levels of -115GG homozygotes did not correlate with dietary cholesterol intake, suggesting that LXRα gene variants have an influence on this association (Robitaille et al., 2007). Zhou et al. linked the same SNP to coronary heart disease in a Chinese Han population. They found that carriers of the AA or GA genotype had a 1.76 fold higher risk of coronary heart disease than carriers of the GG genotype, although the serum lipids and glucose levels did not differ between the genotypes (Zhou et al., 2014). In the INVEST-GENES study, the variant A allele of rs12221497 was shown to confer a reduced risk to experience the primary outcome, which was first occurrence of all-cause death, nonfatal myocardial infarction or nonfatal stroke, in Non-Blacks. People participating in the study either received verapamil-SR or atenolol as antihypertensive therapy. Price et al. further investigated the influence of the treatment strategy on the protective effect provided by the variant A allele of rs12221497 and found that only the participants subjected to the verapamil-SR treatment strategy had a significantly reduced risk for experiencing the primary outcome, whereas this was not the case for patients treated with atenolol (Price et al., 2011).

Sabatti et al. showed that the variant alleles of two other NR1H3 SNPs (rs2167079 and rs7120118) were associated with an increase in HDL levels (Sabatti et al., 2009).

The A allele of the NR1H3 SNP rs11039155 (-6G > A) was associated with a reduced risk of metabolic syndrome in two independent French populations. Furthermore, subjects with the -6A allele had higher plasma HDL cholesterol levels in comparison to -6GG subjects. Notably, this SNP was not significantly associated with plasma triglyceride levels (Legry et al., 2008).

In regard to LXRβ, the minor allele of the SNP rs2248949 has been associated with a decrease in insulin secretion and an alteration in insulin processing in subjects at increased risk for type 2 diabetes, linking this SNP to pancreatic β-cell dysfunction (Ketterer et al., 2011).

Moreover, some studies showed an association between SNPs in the LXRα and LXRβ genes and obesity (Dahlman et al., 2006; Solaas et al., 2010). Interestingly, Solaas et al. uncovered an opposing effect of the LXRβ SNP rs17373080 on obesity and type 2 diabetes. They showed that carriers of the minor G allele had a higher risk of obesity or overweight in the MONICA (France) and HELENA (Europe) studies, respectively, but suggested a lower risk of type 2 diabetes for subjects with this minor allele (HUNT2 study (Norway)) (Solaas et al., 2010).

The SNPs LB44732G > A and rs2695121 (C > T), both found in the LXRβ gene, were nominally associated with obesity. The AA genotype, but not the heterozygous genotype, of LB44732G > A seems to have a recessive protective effect concerning obesity, since it was more common among the controls than among the cases. Concerning rs2695121, the CC genotype, but not the CT genotype, seems to have a recessive protective impact on obesity, since it was more common among the non-obese than among the obese (Dahlman et al., 2006).

As mentioned above, inflammation is also implicated in the development of atherosclerosis. Though no literature is available concerning genetic variations of LXR and inflammatory processes in atherosclerosis, polymorphisms of LXR have been linked to several other inflammatory diseases.

Wang et al. identified the LXRα variant rs61731956 (c.1244G > A, p.Arg415Gln) being present in seven multiple sclerosis (MS) patients from two unrelated families, who suffered from a very severe and progressive form of this disease. They further associated the minor allele of the NR1H3 variant rs2279238 with a higher risk of developing progressive MS (Wang et al., 2016).

Jeon et al. investigated the association of polymorphisms in the NR1H3 promoter with systemic lupus erythematosus, an autoimmune disease, in Korean patients. They linked the rare alleles of -1830T > C, -1003G > A and -115G > A with higher disease susceptibility (Jeon et al., 2014).

Moreover, an association between LXRβ gene polymorphisms and the risk for inflammatory bowel disease was found. Andersen et al. showed that homozygous carriers of the variant genotype rs2695121 (T > C) had a higher risk of ulcerative colitis than homozygous wild-type carriers. Among people who had never smoked, the authors found an association between the variant genotypes of rs1405655 (T > C) and rs2695121 (T > C) and risk of inflammatory bowel disease (Andersen et al., 2011).

Genetic variants of LXR also have an influence on the phenotype of amyotrophic lateral sclerosis (ALS) and on the progression of Alzheimer's disease (AD). Mouzat et al. revealed an association between two LXRα SNPs (rs2279238 and rs7120118) and the age at onset of ALS. They also identified an LXRβ SNP (rs2695121) that modulates the duration of ALS (Mouzat et al., 2018). In regard to AD, Natunen et al. showed that the CC genotype of the LXRα SNP rs7120118 (T > C) conferred reduced levels of the amyloid-β peptide Aβ42 in comparison to the TT genotype, suggesting a decrease in the progression of AD in carriers of the CC genotype (Natunen et al., 2013).

In general, it is important to bear in mind that ethnical groups and populations are heterogenic, which might account for differences in the outcome of distinct studies. Further efforts are needed to gain more insight into the association of LXRα and LXRβ genotypes with metabolic diseases.

3. The farnesoid X receptor (FXR)

FXR is a metabolic nuclear receptor mainly expressed in the liver, intestine, kidney and adrenal glands. The name “farnesoid X receptor” originates from its first identified ligand farnesol, an intermediate in the mevalonate biosynthetic pathway (Forman et al., 1995). Later on, the endogenous ligands for this receptor were identified to be bile acids, such as CDCA and CA, classifying FXR as nuclear bile acid receptor (Makishima et al., 1999).

There are two different FXR genes known, FXRα (NR1H4) and FXRβ (NR1H5), which exhibit a strong homology to each other. Both genes have been shown to encode for functional proteins in mice, rats, dogs and rabbits. In humans and primates, only FXRα encodes a functional protein, whereas FXRβ is a pseudogene. In mice, FXRβ is activated by lanosterol, an intermediate in cholesterol synthesis, and thought to be important in embryonal development and reproduction. Additionally, FXRβ seems to have overlapping functions with FXRα in mice (Otte et al., 2003).

For the purpose of this review, FXRα will be simplified to FXR as FXRβ is not relevant in humans.

FXR is able to bind the response elements of target genes (FXRE) as monomer, homodimer or heterodimer with RXR as partner (Claudel

et al., 2002). FXREs can contain an inverted repeat sequence (IR-1), direct repeats (DR-1) and everted repeats (ER-8) (Gadaleta et al., 2015). The FXR/RXR heterodimer is permissive, meaning it can be activated either by binding of an FXR ligand or an RXR ligand (Leblanc and Stunnenberg, 1995).

3.1. The role of FXR in metabolic processes

3.1.1. Regulation of bile acid metabolism

Multiple *in vivo* and *in vitro* studies were able to link activation of FXR to modulated bile acid metabolism. Not only bile acid synthesis is influenced by FXR but also the enterohepatic circulation of bile acids. Activation of FXR leads to the suppression of CYP7A1 transcription, the key enzyme in bile acid synthesis. The transcription of cytochrome P450 8B1 (CYP8B1), the enzyme important for cholic acid synthesis, is also inhibited by FXR. Activation of FXR in the liver leads to enhanced expression of small heterodimer partner (SHP, NR0B2) which in turn interacts with hepatocyte nuclear factor 4 α (HNF4α) and liver receptor homolog-1 (LRH-1). Interaction of SHP with LRH-1 leads to repression of CYP7A1 and SHP itself, as a feedback loop (Goodwin et al., 2000; Lu et al., 2000). On the other hand, SHP-mediated repression of HNF4α leads to an inhibition of CYP8B1 (del Castillo-Olivares et al., 2004; Goodwin et al., 2000; Lu et al., 2000; Trauner et al., 1998; Zhang and Chiang, 2001). FXR activation in the intestine leads to expression and release of the fibroblast growth factor 19 (FGF19, FGF15 in rodents) which travels *via* the enterohepatic circulation to the liver where it binds fibroblast growth factor receptor 4 (FGFR4) (Holt et al., 2003). Activation of FGFR4 then acts *via* extracellular signal-regulated protein kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase 1/2 (JNK1/2) to inhibit both CYP7A1 and CYP8B1 expression (Holt et al., 2003; Kong et al., 2012; Song et al., 2009). FGF19 also has a minor contribution to SHP activation *via* FGFR4 (Kong et al., 2012; Song et al., 2009).

FXR is also essential for the regulation of genes important for bile acid conjugation such as bile acid CoA synthase (BACS) and bile acid CoA amino acid N-acetyltransferase (BAAT) (Pircher et al., 2003). Moreover, FXR regulates genes for bile acid transport. Sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) and organic anion transporting polypeptide (OATP, SLCO1A2), two transporters important for bile acid import into the liver, are suppressed by FXR. On the other hand bile salt export pump (BSEP) and multidrug resistance-associated protein 2 (MRP2), two transporters involved in bile acid export out of the liver, are increased by FXR (Calkin and Tontonoz, 2012). Furthermore, FXR increases the expression of multidrug resistance protein 3 (MDR3), which secrets phospholipids to the bile canaliculi, thereby promoting the formation of mixed micelles and decreasing bile acid toxicity (Huang et al., 2003). Activation of FXR increases the expression of the enzymes cytochrome P450 3A4 (CYP3A4), the sulfotransferase 2A1 (SULT2A1) and the UDP-glucuronosyltransferase family 2 member B4 (UGT2B4) (Gnerre et al., 2004; Song et al., 2001). These enzymes are decreasing the toxicity of hydrophobic bile acids *via* oxidation, sulfation, and glucuronidation (Lee et al., 2010). In the enterocyte, FXR increases the apical sodium-dependent bile acid transporter (ASBT, SLC10A2, IBAT), which is important for the reabsorption of bile acids from the intestinal lumen, as well as ileal bile acid binding-protein (IBABP, gastrotropin) and organic solute transporter α/β (OSTα/β), which are both important for the transcellular bile acid transport (Calkin and Tontonoz, 2012; Makishima et al., 1999; Neimark et al., 2004; Zollner et al., 2006).

3.1.2. Influence on lipid and glucose metabolism

FXR KO mice display elevated cholesterol and triglyceride levels, highlighting the relevance of FXR in lipid metabolism (Sinal et al., 2000). FXR has been reported to regulate the expression of many genes involved in these processes, like APOC2, APOC3, and the VLDL receptor. Activation of FXR leads to repression of *de novo* lipogenesis *via* activation of SHP and subsequent downregulation of SREBP-1c mRNA in the liver (Watanabe et al., 2004). Additionally, an IR-1 site has been identified in the fatty acid synthase promoter, making it a likely target gene of FXR (Calkin and Tontonoz, 2012; Matsukuma et al., 2006).

Recently, several studies have been performed investigating the effects of FXR on hepatic glucose metabolism, suggesting several genes relevant in gluconeogenesis like phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase) and fructose-1,6-bisphosphatase to be regulated by FXR (De Fabiani et al., 2003; Ma et al., 2006; Stayrook et al., 2005; Yamagata et al., 2004; Zhang et al., 2006).

3.2. FXR as therapeutic target

Due to their broad spectrum of effects, FXR agonists have therapeutic potential in metabolic diseases such as hypercholesterolemia, hypertriglyceridemia, nonalcoholic steatohepatitis and type 2 diabetes mellitus (De Magalhaes Filho et al., 2017). Moreover, FXR agonists are used in the therapy of cholestatic liver diseases, like primary biliary cirrhosis (PBC), and are investigated for the use in primary sclerosing cholangitis and intrahepatic cholestasis of pregnancy (Fuchs et al., 2016; Kim et al., 2016; Oseini and Sanyal, 2017). Furthermore, FXR agonists could be used in the treatment of atherosclerosis as two agonists, obeticholic acid and WAY-362450, reduced aortic plaque formation in mouse models (Hartman et al., 2009; Mencarelli et al., 2009). The use of FXR agonist in the treatment of bile acid diarrhea also seems to have therapeutic potential (Keely and Walters, 2016).

3.3. Natural product-derived ligands for FXR

The endogenous ligands of FXR are bile acids. The most potent FXR activating bile acid is CDCA (Table 2), with an EC_{50} of 10 μM in a cell-based FXR transactivation assay, followed by DCA, lithocholic acid (LCA), and finally CA (Makishima et al., 1999). However, bile acids also act as ligands for the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), the vitamin D receptor (VDR) and the G-protein coupled receptor TGR5 (GPBAR1). Therefore, many efforts were undertaken to generate more specific FXR modulators. One of them is obeticholic acid (6-ECDCA; 6α-ethyl-chenodeoxycholic acid; INT-747) a synthetic derivative of CDCA. This potent FXR agonist (EC_{50} of 99 nM in an FXR transactivation assay) has been and is currently investigated in several clinical trials (http://www.clinicaltrials.gov; Nevens et al., 2016; Pellicciari et al., 2002; Schaap et al., 2014). Obeticholic acid has been approved as a drug for pimary biliary cholangitis in the US and Europe in 2016 in a fast track procedure.

The most potent synthetic FXR agonist, with an EC_{50} of 90 nM in an FXR transactivation assay, is GW4064 containing a stilbene structure, which harbors the risk for toxic side effects. Moreover, the bioavailability of GW4064 is very low and the half-life very short (Akwabi-Ameyaw et al., 2008; Akwabi-Ameyaw et al., 2009; Maloney et al., 2000).

Farnesol (Table 2), the compound that gave FXR its name, was the first FXR ligand identified. Farnesol is a very weak agonist in the high micromolar range and a common natural product present in many essential oils. It is produced via the isoprene biosynthesis pathway in plants and animals (Forman et al., 1995).

A very well established FXR ligand from a natural source is guggulsterone, with the two stereoisomers *E*-guggulsterone and *Z*-guggulsterone (Table 2) showing similar potency in several studies, however most studies focused on *Z*-guggulsterone (Cui et al., 2003; Urizar et al., 2002; Wu et al., 2002). This compound is the main bioactive constituent of the gum resin of *Commiphora mukul*, which has been used in Ayurvedic medicine since several thousand years against a variety of illnesses including obesity and lipid disorders. Guggulsterone has initially been described as FXR antagonist, by blocking the interaction between FXR and coactivators (Urizar et al., 2002; Wu et al., 2002), but has also been reported to increase the expression of BSEP (Cui et al., 2003). Both actions have been suggested for being responsible for the

Table 2
Natural products modulating FXR activity.

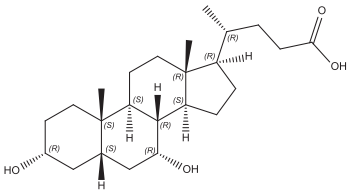
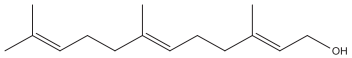
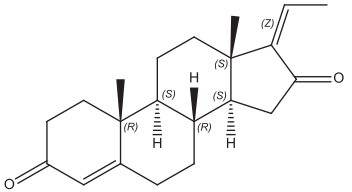
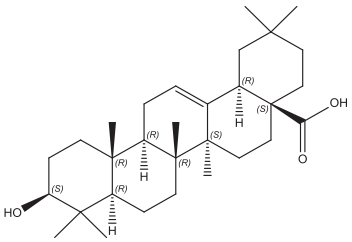
Natural product	Test system	Potency / Efficacy	Reference
Chenodeoxycholic acid (CDCA) Endogenous agonist 	Transactivation activity in a reporter gene assay (rat FXR, hFXR)	FXRE promoter: EC_{50} 10 μM (human) EC_{50} 50 μM (murine) hCYP7A1 promoter: EC_{50} 20 μM Enhanced transactivation on mIBABP promoter	(Makishima et al., 1999)
	Binding activity by measuring ligand-dependent coactivator recruitment	EC_{50} 10 to 20 μM	
	Target gene expression studies (mRNA, protein)	HepG2: CYP7A1	
Farnesol Agonist 	Transactivation activity in a reporter gene assay (rat FXR)	Enhanced transactivation at 50 μM	(Forman et al., 1995)
Z-guggulsterone SBARM 	Transactivation activity in a reporter gene assay (mFXR)	Repressive effect on FXRE, hSHP, and mIBABP (tested at 10–100 μM with 100 μM CDCA) Enhanced transactivation on BSEP E_{max} 200% of 100 nM GW4064, and 4 fold without agonist cotreatement	(Burris et al., 2005; Cui et al., 2003; Urizar et al., 2002; Wu et al., 2002)
	Binding activity in a mammalian one – hybrid assay	IC_{50} 1–5 μM E_{max} 100% inhibition at 10 μM No effect on LXRα, PPARγ, and RXRα. Inhibition of PPARα and PXR at 10 μM (Urizar et al., 2002). Weak antagonist of LXRs, PPARs CAR and RXR E_{max} of 25–40% at 10 μM. No activity in agonist mode except for PXR (Wu et al., 2002).	
	Binding activity by measuring ligand-dependent coactivator recruitment	Guggulsterone alone does not recruit SRC-1, p120, PBP, and TRAP220; addition of guggulsterone blocked CDCA-dependent coactivor binding to FXR with an IC_{50} of 17 μM for SRC-1, 6.6 μM for p120, 9.9 μM for PBP, and 0.1–1 μM for TRAP220 Displacement of RXR and LXR bound coactivators at 10–50 μM	
	Radioligand binding assay	Binding to GR: (E)-GS K_i 252 ± 6 nM (Z)-GS K_i 224 ± 26 Binding to MR: (E)-GS K_i 37 ± 2 nM (Z)-GS K_i 39 ± 4 Binding to AR: (E)-GS K_i 315 ± 13 nM (Z)-GS K_i 240 ± 21 Binding to PR: (E)-GS K_i 224 ± 6 nM (Z)-GS K_i 201 ± 18 No binding on ERα, ERβ, FXR, LXRα, TRα, TRβ, PPARα, PPARδ, PPARγ, and RXRα	
	Target gene expression (mRNA)	Primary mouse hepatocytes: SHP (tested at 10–100 μM with 100 μM CDCA) Caco-2: IBABP (tested at 10–200 μM with 100 μM CDCA) HepG2: BSEP (tested at 0.3–50 μM with 25 μM CDCA or 100 nM GW4064) E_{max} 400–500% of 25 μM CDCA; no effect on BSEP mRNA without agonist cotreatment; SHP (tested at 1–10 μM with 100 μM CDCA) No effect on ABCA1 and ABCG1	
	In vivo FXR KO studies	FXR-dependent decrease in hepatic cholesterol levels at 100 mg/kg body weight	
Oleanolic acid Antagonist 	Binding activity in a mammalian one-hybrid assay	Repressive effect (tested at 5–50 μM with 25 μM CDCA); no effect without agonist cotreatment and on LXRα and LXRβ in antagonist mode	(Liu and Wong, 2010; Sato et al., 2007)
	Transactivation activity in a reporter gene assay (TGR5)	EC_{50} 1.42 μM	
	Surface plasmon resonance (SPR) analysis	Repressive effect (tested at 25 μM with 50 μM CDCA) for SRC-3	
	Target gene expression (mRNA)	HepG2: BSEP, OSTβ, SHP and CYP7A1	

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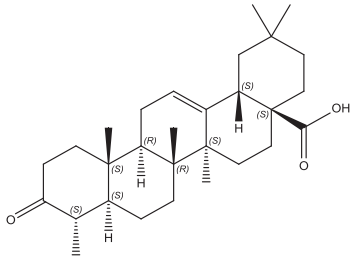
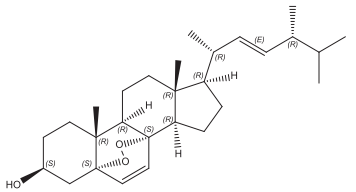
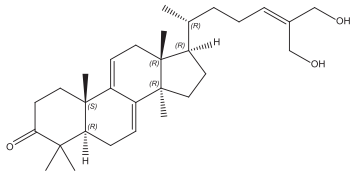
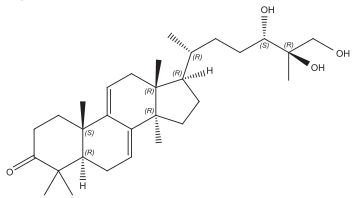
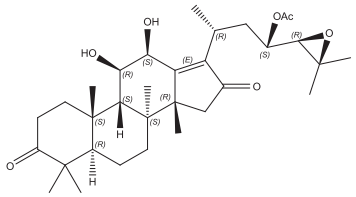
Table 2 (*continued*)

Natural product	Test system	Potency / Efficacy	Reference
Hedragonic acid Agonist 	Coregulator binding assays (AlphaScreen) Transactivation activity in a reporter gene assay Circular dichroism (CD) spectroscopy Crystal structure anaysis Functional studies	SRC1-2, SRC2-3, and SRC3-3 recruited, NCoR not recruited Enhanced transactivation at 1 μM for EcRE No effect on PPARα, PPARδ, PPARγ, AR, GR, RARα, RARβ, RORα, RORβ, and RORγ Weak activity on TGR5 Conformational changes in FXR-LBD induces similar than GW4064 of FXR complexed with hedragonic acid FXR dependent protection from liver injury by acetaminophen	(Lu et al., 2018)
Ergosterol peroxide Agonist 	Transactivation activity in a reporter gene assay (mFXR) Target gene expression (mRNA)	Enhanced transactivation at 0.1–20 μM for EcRE EC_{50} 0.85 μM HepG2: CYP7A1	(Grienke et al., 2011)
Ganoderiol F Agonist 	Transactivation activity in a reporter gene assay (mFXR) Target gene expression (mRNA)	Enhanced transactivation at 0.1–20 μM on EcRE EC_{50} 5 μM HepG2: CYP7A1	(Grienke et al., 2011)
Ganodermanontriol Agonist 	Transactivation activity in a reporter gene assay (mFXR) Target gene expression (mRNA)	Enhanced transactivation at 0.1–20 μM on EcRE EC_{50} 2.5 μM HepG2: CYP7A1	(Grienke et al., 2011)
Alisol M 23-acetate Agonist 	Transactivation activity in a reporter gene assay (FXR) Binding activity in a mammalian one – hybrid assay	Enhanced transactivation at 0.1–10 μM on the SHP, CYP7A1 and PLTP promoter Enhanced transactivation at 0.1–10 μM	(Lin, 2012)

(*continued on next page*)

Table 2 (*continued*)

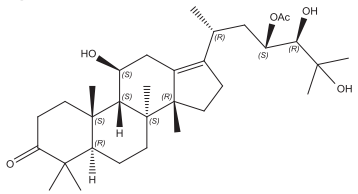
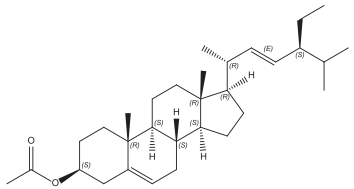
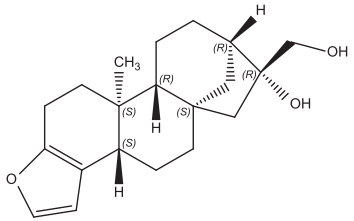
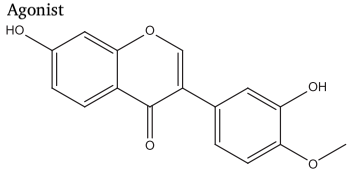
Natural product	Test system	Potency / Efficacy	Reference
Alisol A 23-acetate Agonist 	Transactivation activity in a reporter gene assay (FXR)	Enhanced transactivation at 0.1–10 μM on the SHP, CYP7A1 and PLTP promoter	(Lin, 2012)
	Binding activity in a mammalian one – hybrid assay	Enhanced transactivation at 0.1–10 μM	
Stigmasterol acetate Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	Repressive effect on EcRE at 5 and 10 μM with 100 μM CDCA	(Carter et al., 2007)
	Binding activity in a mammalian one – hybrid assay	Repressive effect 5 and 10 μM with 100 μM CDCA Additional repressive effect on PXR at 10 μM	
	Target gene expression (mRNA)	HepG2: BSEP, FGF19, OSTα, and OSTβ	
	In vivo FXR KO studies	Hepatocytes derived from FXR WT and KO mice: decrease in SHP and BSEP mRNA abrogated in KO animals	
Cafestol Agonist 	Binding activity in a mammalian one – hybrid assay	Enhanced transactivation at 20 μM for FXR and mPXR	(Ricketts et al., 2007)
	Transactivation activity in a reporter gene assay (hFXR, mFXR)	Enhanced transaction at 1–100 μM on the BSEP and IBABP promoter	
	Mammalian two hybrid assay (mSRC-1)	Enhanced recruitment at 1–20 μM	
	In vivo FXR KO studies	Tested at 400 mg/kg body weight for CYP7A1, CYP8B1, NTCP, SHP, BSEP, and IBABP mRNA expression	
Calycosin Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation on the BSEP promoter at 1–10 μM	(Chen et al., 2015; Duan et al., 2017)
	Hepatic steatosis mouse model	Enhanced SHP, CYP7A1, and BSEP mRNA expression at 12.5–50 mg/kg	

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Table 2 (*continued*)

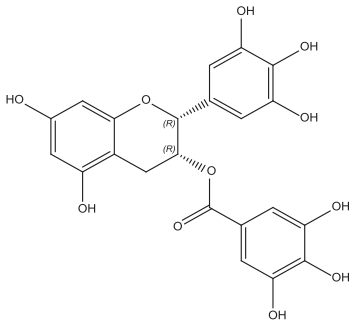
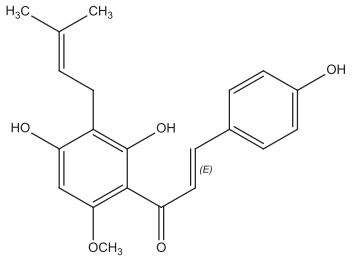
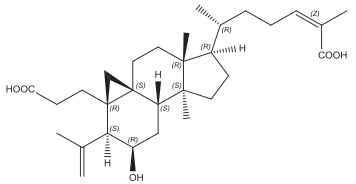
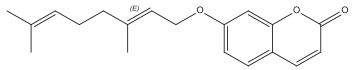
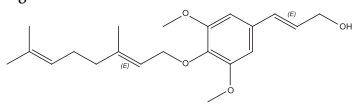
Natural product	Test system	Potency / Efficacy	Reference
Epigallocatechin-3-gallate (EGCG) SBARM 	Transactivation activity in a reporter gene assay (hFXR) Target gene expression (mRNA) Binding activity by measuring ligand-dependent coactivator recruitment (FRET) *In vivo* FXR KO studies	Enhanced transactivation at 0.01–100 μM on the SHP promoter EC_{50} 2.99 μM E_{max} 7 to 9-fold increase HepG2: SHP, OSTα, and BSEP in agonistic setting (enhanced expression for SHP and BSEP) SHP, OSTα, OSTβ and BSEP in antagonistic setting (500 nM GW4064 and 100 μM CDCA - decreased expression for all tested genes) No recruitment of SRC2 to FXR by EGCG alone but inhibition of GW4064-mediated recruitment IC_{50} 1 μM Tested at 100 mg/kg P.O. or 25 mg/mg I.P. for FXR, SHP, IBABP, and FGF19 mRNA expression	(Li et al., 2012)
Xanthohumol SBARM 	Transactivation activity in a reporter gene assay (hFXR) Diabetic mouse model	Enhanced transactivation at 0.5–20 μM on the BSEP promoter 5.6 ± 0.6 fold activation at 10 μM Tested at 0.3–1% xanthohumol rich extract for SHP, CYP7A1 and BSEP mRNA expression amongst others	(Nozawa, 2005)
6β-hydroxynigranoic acid Antagonist 	Yeast two-hybrid system-based assay with FXR-LBD and SRC-1	IC_{50} 1.5 μM with an inhibition rate of 92.9% at 25 μM (tested with 10 μM CDCA)	(Zou et al., 2012a; Zou et al., 2012b)
Auraptene Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 0.1–100 μM on FXRE	(Epifano et al., 2012)
Nelumol A Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 0.1–100 μM on FXRE	(Epifano et al., 2012)

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Table 2 (*continued*)

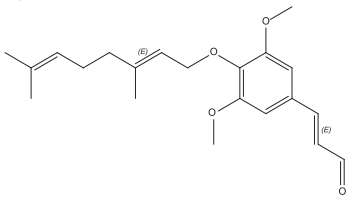
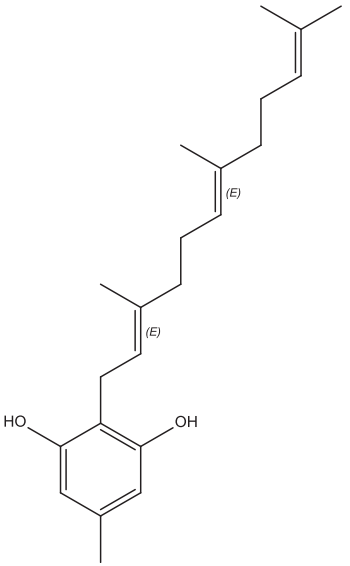
Natural product	Test system	Potency / Efficacy	Reference
Nelumal A Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 0.1–100 μM on FXRE	(Epifano et al., 2012)
Grifolin Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 30 μM on FXRE	(Suzuki et al., 2006)

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Table 2 (*continued*)

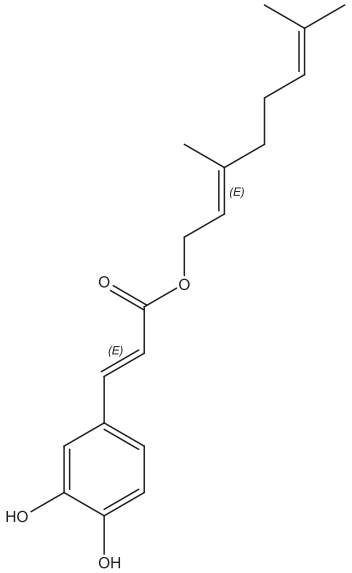
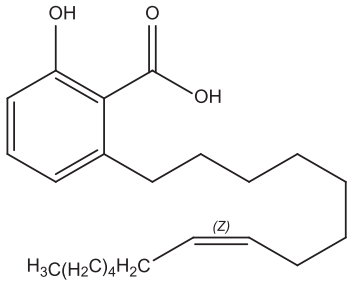
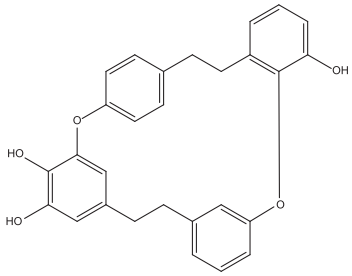
Natural product	Test system	Potency / Efficacy	Reference
Geranyl caffeate Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 30 µM on FXRE Additional activity on RARα, RARβ, and RARγ	(Suzuki et al., 2006)
Ginkgolic acid 15:1 Agonist 	Transactivation activity in a reporter gene assay (hFXR) Target gene expression (mRNA)	Enhanced transactivation at 1–60 µM on FXRE HepG2: SHP, BSEP, CYP7A1 HuH-7: BSEP	(Suzuki et al., 2006; Suzuki et al., 2008)
Marchantin A SBARM 	Transactivation activity in a reporter gene assay (hFXR) Target gene expression (mRNA)	Enhanced transactivation at 0.1–10 µM on FXRE EC_{50} 3–6 µM E_{max} 40% of CDCA HepG2: SHP, BSEP, CYP7A1 HuH-7: BSEP	(Suzuki et al., 2008)

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Table 2 (*continued*)

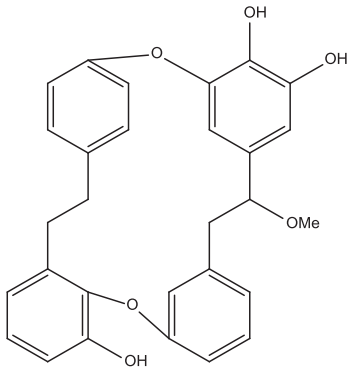
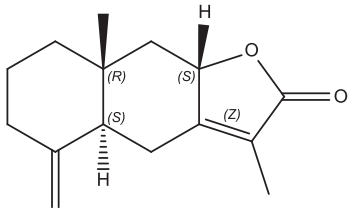
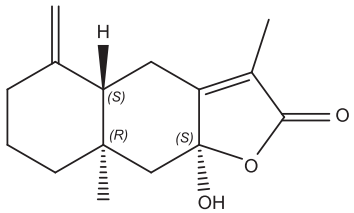
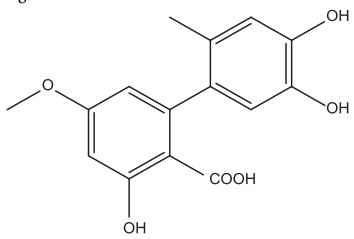
Natural product	Test system	Potency / Efficacy	Reference
Marchantin E SBARM 	Transactivation activity in a reporter gene assay (hFXR) Target gene expression (mRNA)	Enhanced transactivation at 0.1–10 μM on FXRE EC_{50} 3–6 μM E_{max} 55% of CDCA HepG2: SHP, BSEP, CYP7A1 HuH-7: BSEP	(Suzuki et al., 2008)
Atractylenolide II Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	Repressive effect at 10–100 μM with 10 μM CDCA on the SHP and enhancing effect alone on the CYP7A1 promoter	(Tsai et al., 2012)
Atractylenolide III Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	Repressive effect at 10–100 μM with 10 μM CDCA on the SHP and enhancing effect alone on the CYP7A1 promoter	(Tsai et al., 2012)
Altenusin Agonist 	Binding activity in a mammalian one – hybrid assay Transactivation activity in a reporter gene assay (hFXR) Target gene expression (mRNA) *In vivo* FXR KO studies	EC50 3.4 ± 0.2 μM – similar potency and efficacy than CDCA Enhanced transactivation at 25–50 μM on the EcRE promoter Primary hepatocytes from FXR WT and KO mice: SHP, BSEP, SR-BI, CYP7A1 High fat diet induced obesity model: FXR dependent weight and fat loss, reversal of pre-existing hepatic steatosis, reduced plasma glucose and insulin levels Gene expression analysis	(Zheng et al., 2017)

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Table 2 (*continued*)

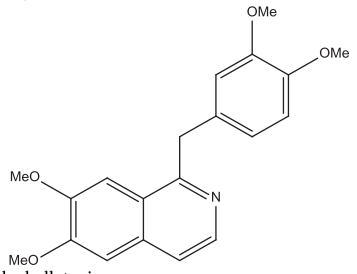
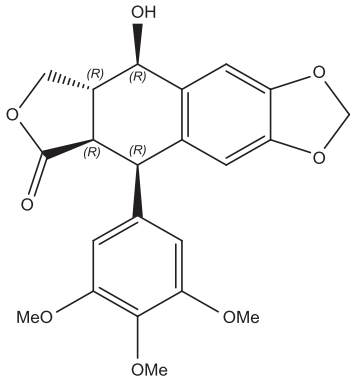
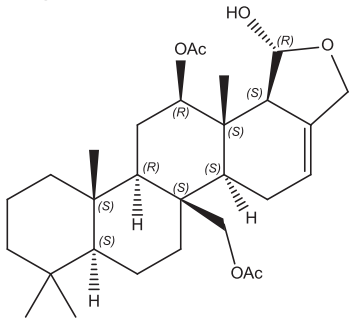
Natural product	Test system	Potency / Efficacy	Reference
Papaverine Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 10 μM on BSEP promoter; FXR activation at 10 μM 13.3 ± 1.9% of 3 μM GW4064	(Steri et al., 2012)
Podophyllotoxin Agonist 	Transactivation activity in a reporter gene assay (hFXR)	Enhanced transactivation at 10 μM on BSEP promoter	(Steri et al., 2012)
12,24-diacetoxy-deoxoscalarin Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	Repressive effect on the EcRE promoter with an IC_{50} of 8.1 μM (with 50 μM CDCA)	(Nam et al., 2006)

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Table 2 (*continued*)

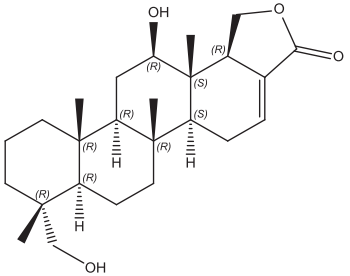
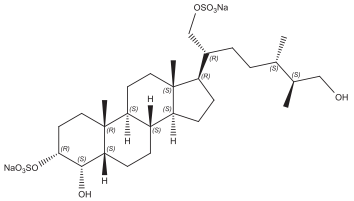
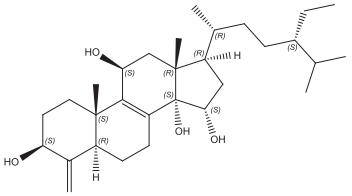
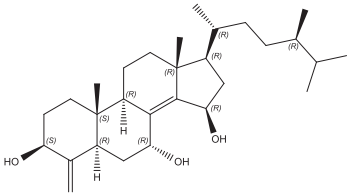
Natural product	Test system	Potency / Efficacy	Reference
12-*O*-deacetyl-12-*epi*-19-deoxy-21-hydroxyscalarin Antagonist 	Transactivation activity in a reporter gene assay (hFXR) Surface plasmon resonance (SPR) analysis	Repressive effect on the EcRE promoter with an IC_{50} 2.4 μM (with 50 μM CDCA) Weak inhibition at 25 μM with 50 μM CDCA on SRC-1	(Nam et al., 2007)
Ergostane-3,4,21,26-tetrol,3,21-bis(hydrogen sulfate), (3α,4α,5β,25*S*) Antagonist 	Transactivation activity in a reporter gene assay (FXR) Target gene expression (mRNA)	Repressive effect on IR-1 response elements from HSP27 at 50 and 100 μM together with 10 μM CDCA HepG2: BSEP, OSTα, OSTβ and CYP7A1	(Sepe et al., 2011)
Theonellasterol G SBARM 	Transactivation activity in a reporter gene assay (FXR) Target gene expression (mRNA)	Enhanced transactivation on IR-1 response elements from HSP27 at 10 μM Repressive effect on IR-1 response elements from HSP27 at 50 μM with 10 μM CDCA Enhanced transactivation of PXR at 10 μM and repressive effect at 50 μM with 10 μM Rifaximin HepG2: BSEP, OSTα	(De Marino et al., 2011)
Conicasterol E SBARM 	Transactivation activity in a reporter gene assay (FXR) Target gene expression (mRNA)	Enhanced transactivation (bell-shaped) on IR-1 response elements from HSP27 at 1–50 μM Enhanced transactivation of PXR at 10 μM HepG2: BSEP, SHP, OSTα, and CYP7A1	(Sepe et al., 2012)

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Table 2 (*continued*)

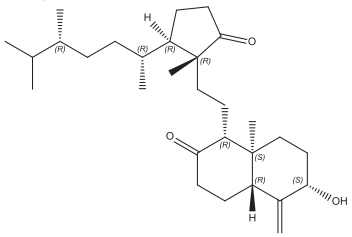
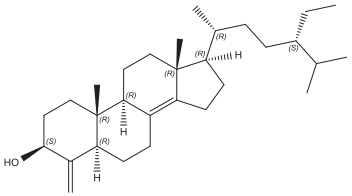
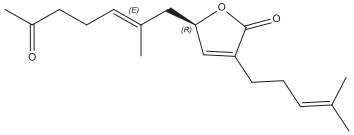
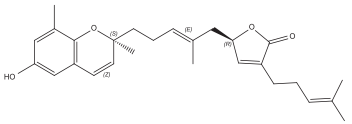
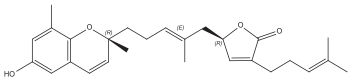
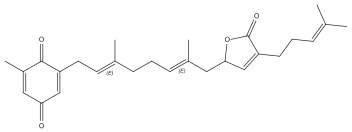
Natural product	Test system	Potency / Efficacy	Reference
Swinhosterol B Antagonist 	Transactivation activity in a reporter gene assay (FXR)	Repressive effect on IR-1 response elements from HSP27 at 10–50 μM with 10 μM CDCA Enhanced transactivation of PXR at 10 μM	(De Marino et al., 2012)
	Target gene expression (mRNA)	HepG2: BSEP, SHP, OSTα, and CYP7A1	
Theonellasterol Antagonist 	Transactivation activity in a reporter gene assay (FXR)	Repressive effect on IR-1 response elements from HSP27 at 50 μM	(Renga et al., 2012)
	Corepressor interaction assay	Stabilizationof NCoR at 50 μM	
	Target gene expression (mRNA)	HepG2: BSEP, SHP, OSTα, MRP4, different nuclear receptor mRNAs	
	Binding activity in a mammalian one – hybrid assay	No effect on PPARγ, PXR, VDR and GR at 10 μM	
	Mouse model for obstructive cholestasis	Decreased serum ALT and necrotic foci; reduced mRNA expression of OSTα and SHP and increased MRP4 expression; Tested at 10 mg/kg	
Tuberatolide A Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 3.9 μM	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	
Tuberatolide B Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 1.5 μM (with 50 μM CDCA)	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	
2′-*epi*-tuberatolide B Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 2.5 μM (with 50 μM CDCA)	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	
Yezoquinolide Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 5.9 μM (with 50 μM CDCA)	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	

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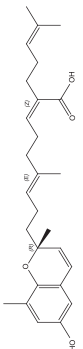
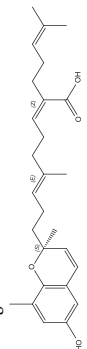
Table 2 (*continued*)

Natural product	Test system	Potency / Efficacy	Reference
(R)-sargachromenol Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 9.0 μM (with 50 μM CDCA)	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	
(S)-sargachromenol Antagonist 	Transactivation activity in a reporter gene assay (hFXR)	EcRE promoter: IC_{50} 17 μM (with 50 μM CDCA)	(Choi et al., 2011)
	Surface plasmon resonance (SPR) analysis	Decreased binding affinity of SRC-1 to FXR-LBD at 25 μM with 50 μM CDCA	

hypolipidemic effects of guggulsterone. Therefore, guggulsterone can more accurately be described as selective bile acid receptor modulator (SBARM). In a Gal4-responsive luciferase reporter gene assay guggulsterone was able to antagonize FXR with an IC_{50} of 1–5 μM (Wu et al., 2002). Guggulsterone is, however, not specific. A potent antagonistic effect on the mineralocorticoid receptor, glucocorticoid receptor, and androgen receptor and agonistic effect on the PXR, progesterone receptor, and estrogen receptor have been reported (Brobst et al., 2004; Burris et al., 2005; Owsley and Chiang, 2003). In addition, guggulsterone is a potent inhibitor of the nuclear factor κB granting it anti-inflammatory activity (Cheon et al., 2006; Ichikawa and Aggarwal, 2006; Li et al., 2015; Shishodia and Aggarwal, 2004).

The pentacyclic triterpene acid, oleanolic acid (Table 2), is widely distributed in the plant kingdom. Oleanolic acid has been described as FXR antagonist at 10 μM, by binding to the LBD of FXR and blocking its ability to interact with the coactivator SRC-3. Interestingly, oleanolic acid was able to enhance the expression of SHP, thereby inhibiting the expression of CYP7A1 (Liu and Wong, 2010). Apart from its activity on FXR, oleanolic acid is a potent activator of TGR5 (Sato et al., 2007).

Recently another natural triterpene, hedragonic acid (Table 2), isolated from the stem and roots of *Celastrus orbicalatus* Thunb., has been identified to act as FXR agonist in coregulator binding assays as it was able to recruit SRC-1, SRC-2 and SRC-3 coactivators, however not NcoR corepressors. Using circular dichroism (CD) spectroscopy, they could detect conformational changes of the FXR-LBD with hedragonic acid similar to GW4064. Additionally, hedragonic acid activated FXR but not PPARα/δ/γ, retinoic acid receptor (RAR) α, RAR-related orphan receptor (ROR) α/β/γ, androgen receptor (AR) and glucocorticoid receptor (GR) in luciferase reporter gene assays. The crystal structure of hedragonic acid bound FXR revealed a novel binding site and compared the molecular basis for TGR5 and FXR binding (Lu et al., 2018).

Lanostane-type triterpenes from the fruiting bodies of the fungus *Ganoderma lucidum* have been shown to possess FXR agonistic activity in a luciferase reporter gene assay as well as in regard to the mRNA expression of the FXR target gene CYP7A1. To investigate the binding mode, molecular docking studies were performed. The three most active compounds ergosterol peroxide, ganoderiol F and ganodermanontriol (Table 2) were able to transactivate FXR with EC_{50}s of 0.85, 5 and 2.5 μM, respectively (Grienke et al., 2011).

Two triterpenes from *Alisma orientalis*, alisol M 23-acetate and alisol A 23-acetate (Table 2), were identified to transactivate FXR at a concentration of 1 μM and to modulate the expression of genes like SHP and CYP7A1 (Lin, 2012). Another compound isolated from this plant, alisol B 23-acetate, was investigated in a mouse model for liver regeneration, where it potently increased hepatocyte proliferation and attenuated liver injury by regulating genes for hepatic proliferation, hepatoprotection, bile acid synthesis and transport. Luciferase reporter gene assays showed an increase in the transactivation of the BSEP and SHP promotor upon treatment with this compound (Meng et al., 2015a; Meng et al., 2014; Meng et al., 2015b). Silencing of FXR and co-treatment with guggulsterone abrogated the upregulation of BSEP and SHP (Meng et al., 2014). Taking into account that guggulsterone is an activator of BSEP expression this data has to be considered with care (Cui et al., 2003). In a recent paper, however, alisol B 23-acetate was identified as a specific PXR agonist in a Gal4-responsive luciferase assay, with no activity on an FXR construct (Kanno et al., 2017). As PXR and FXR have many target genes in common, this suggests that alisol B 23-acetate might be a PXR agonist and not an FXR agonist.

Stigmasterol acetate (Table 2), the water soluble derivative of stigmasterol, a common plant sterol, has been shown to antagonize CDCA-activated FXR in a luciferase reporter gene assay at 5 to 10 μM. Apart from FXR, stigmasterol acetate also antagonized PXR in a Gal4-responsive luciferase assay (Carter et al., 2007).

Cafestol (Table 2), found in coffee, has been reported to potently transactivate FXR and PXR in a reporter gene assay, with significant effects already at 1 μM. Moreover, FXR target gene regulation has been

investigated in an FXR KO model (Ricketts et al., 2007).

Calycosin (Table 2), a major active compound in Radix Astragali, which is used for liver protection, has been shown to transactivate FXR in a reporter gene assay starting at 1 μM and to modulate the expression of FXR target genes in a mouse model of hepatic steatosis (Chen et al., 2015; Duan et al., 2017).

Epigallocatechin-3-gallate (EGCG) (Table 2), the well-known green tea catechin, has also been described as FXR modulator, together with (−)-epigallocatechin and (−)-epicatechin-3-gallate. In a cell-based reporter gene assay, EGCG concentration-dependently activated FXR with an EC_{50} of 2.99 μM and increased the expression of SHP and BSEP in HepG2 cells. Interestingly, EGCG did not recruit SRC-2 to FXR but blocked the recruitment of SRC-2 to FXR induced by GW4064 in a coactivator recruitment assay. Moreover, EGCG antagonized GW4064-activated FXR regarding target gene expression and also decreased FXR mRNA levels. An investigation of target gene expression in the liver and the intestine from wildtype and FXR KO mice showed that in the ileum only SHP and FGF15 were influenced by EGCG treatment, whereas IBABP was not altered. In the liver, EGCG showed no effect on mRNA levels of SHP, BSEP and CYP7A1. Taken together, EGCG seems to act as an SBARM (Li et al., 2012).

Xanthohumol (Table 2) from *Humulus lupulus* was also identified as an SBARM, as it is not only able to increase the expression of BSEP in a luciferase reporter assay but also the expression of CYP7A1 in the livers of diabetic mice. Effects with Xanthohumol were observed at concentrations between 2 and 20 μM (Nozawa, 2005).

In a two hybrid system, several lanostane-type and cycloartane-type triterpenes from the stems of *Schisandra glaucescens* have been reported as antagonists of FXR, with 6β-hydroxynigranoic acid (Table 2) as the most potent antagonist with an IC_{50} of 1.50 μM (Zou et al., 2012a; Zou et al., 2012b).

Auraptene from *Citrus aurantium* and nelumal A and nelumol A (Table 2) from *Ligularia nelumbifolia* were shown to transactivate FXR in a cell-based reporter gene assay at concentrations of 10–50 μM (Bruyere et al., 2011; Epifano et al., 2012; Epifano et al., 2007).

In a luciferase reporter gene assay, grifolin, geranyl caffeate and ginkgolic acid 15:1 (Table 2) transactivated FXR between 20 and 30 μM. Grifolin can be found in mushrooms, ginkgolic acid 15:1 in ginkgo leaves, and geranyl caffeate in the Himalayan poplar (Greenaway and Whatley, 1991; Suzuki et al., 2006).

Marchantin A and marchantin E (Table 2) are widespread in liverwort *Marchantia* species and activated FXR in a luciferase reporter assay at a concentration of 10 μM. These two natural products regulated gene expression in a cell-type and gene-specific manner, again marking them as SBARMs (Suzuki et al., 2008).

The two sesquiterpenoids, atractylenolide II and III (Table 2), isolated from *Atractylodes macrocephala*, a plant used in traditonal Chinese medicine, were shown to lower cholesterol levels, amongst others. Both compounds had an antagonistic effect on the SHP and CYP7A1 promoter in cell-based reporter assays at concentrations between 10 and 100 μM (Tsai et al., 2012).

Altenusin (Table 2) is a non-steroidal fungal metabolite that has been identified to be a potent FXR agonist in a Gal4-responsive luciferase reporter gene assay with an EC_{50} of 3.4 μM. In addition, altenusin protected mice from high-fat diet-induced obesity by reducing body weight and fat mass. It also decreased blood glucose and serum insulin levels. Moreover, altenusin nearly reversed high-fat diet-induced hepatic lipid droplet accumulation and macrovesicular steatosis. All these effects were abolished in FXR KO mice (Zheng et al., 2017).

Papaverine (Table 2), found in opium poppy, is an approved antispasmodic drug, and podophyllotoxin (Table 2), found in the rhizomes of *Podophyllum* species, is a drug used against genital warts and molluscum contagiosum. Both drugs have recently been discovered to transactivate FXR in a luciferase reporter gene assay at 10 μM (Steri et al., 2012).

There have also been several FXR modulators identified from marine sources. Scalarane sesterterpenes, isolated from a sponge belonging to the *Spongia* genus have been shown to inhibit FXR transactivation by CDCA. Specifically, 12,24-diacetoxy-deoxoscalarin and 12-*O*-deacetyl-12-*epi*-19-deoxy-21-hydroxyscalarin (Table 2) were the most active ones, with IC_{50}s of 8.1 and 2.4 μM, respectively (D'Auria et al., 2012; Nam et al., 2007; Nam et al., 2006).

Sulfated sterols isolated from *Ophiocoma* species have been identified to antagonize FXR transactivation by CDCA, however, in very high concentrations (50 μM). Ergostane-3,4,21,26-tetrol, 3,21-bis(hydrogen sulfate), (3α,4α,5β,25*S*) (Table 2) was the most potent antagonist in this series (Sepe et al., 2011).

Several interesting polyhydroxylated steroids were identified from the marine sponge *Theonella swinhoei* (Table 2). Some of the isolated compounds showed antagonistic activity on CDCA-activated FXR and agonistic activity on PXR in a luciferase reporter assay (De Marino et al., 2012; De Marino et al., 2011). Theonellasterol G was the only compound acting as an antagonist in the presence of CDCA, but also as partial FXR agonist and PXR agonist. Concentrations tested ranged between 10 and 50 μM (De Marino et al., 2011). The same group identified conicasterol E at 50 μM as SBARM inducing the expression of BSEP, OSTα and CYP7A1 without altering SHP (Sepe et al., 2012) and swinhosterol B and theonellasterol between 10 and 50 μM as FXR antagonist in reporter gene and gene expression assays (De Marino et al., 2012; Renga et al., 2012). Theonellasterol additionally elicited hepatoprotective effects in a mouse model of cholestasis (Renga et al., 2012).

Nonsteroidal antagonists of FXR have been isolated from the Korean marine tunicate *Botryllus tuberatus* (Table 2). Tuberatolide A, tuberatolide B, 2′-*epi*-tuberatolide B, yezoquinolide, (*R*)-sargachromenol, and (*S*)-sargachromenol were shown to antagonize CDCA-transactivated FXR in a reporter gene assay with IC_{50}s between 1.5 and 16 μM, and to inhibit binding in a cell-free coactivator recruitment assay (Choi et al., 2011).

A purified *Salvia miltiorrhiza* extract, with salvianolic acid B and rosmarinic acid as main constituents, and an *n*-butanol extract of *Panax notoginseng*, which contains dammarane-type saponins, were shown to activate FXR and LXRα and had hypolipidemic effects in rats fed a high-fat diet. The *Salvia miltiorrhiza* extract transactivated FXR and LXRα with an EC_{50} of 0.66 μg/ml and 1.02 μg/ml, respectively, and the *Panax notoginseng* extract was effective between 50 and 200 μg/ml in the same assay (Ji and Gong, 2007, 2008).

A grape seed procyanidin extract has been demonstrated to transactivate FXR between 20 and 100 μg/ml, but only if already activated by CDCA and not by GW4064, strongly suggesting that procyanidins present in the extract or their metabolites directly bind to CDCA-bound FXR to enhance its transcriptional activity. The specific procyanidins eliciting this effect were, however, not identified (Del Bas et al., 2009). In a recent paper, the same group identified the same extract as SBARM in a mouse model, downregulating genes involved in intestinal bile acid absorption and transport in an FXR-dependent manner. This resulted in decreased enterohepatic bile acid recirculation, increased fecal bile acid loss, decreased serum triglyceride and cholesterol levels, increased hepatic CYP7A1 and decreased FGF15 expression (Heidker et al., 2016).

Similar to this grape seed extract, an extract of California-grown *Deglet Noor* and *Medjool* dates (*Phoenix dactylifera*) did coactivate CDCA-bound FXR between 20 and 100 μg/ml in a Gal4 responsive luciferase assay. However, this effect was not specific as additionally the GR, RARα and RXR were coactivated when treated with the respective agonist. Moreover, agonistic effects were seen on mouse PPARα, mouse PPARγ, and mouse PXR. No activity could be detected for CAR, estrogen receptor (ER) alpha, LXRα, human PXR, thyroid hormone receptor (TR) beta, and VDR. The date palm extract enhanced coactivator recruitment of SRC-1 to CDCA-bound FXR. Target gene expression studies showed that ASBT, IBABP, FGF19 and OSTα were increased when CDCA and date palm extract were cotreated. Interestingly, FXR

expression itself was increased after treatment with this extract alone. (Alfaro-Viquez et al., 2018)

Dichlormethane and methanol extracts of *Ginkgo biloba* leaves, *Vitex agnus-castus* fruits, *Ruta graveolens* roots and leaves, *Capsicum annum* fruits, and *Panax ginseng* roots at 100 μg/ml have been shown to have agonistic FXR activity in a luciferase reporter assay (Grienke et al., 2011).

Sterols from the soft coral *Dendronephthya gigantea* have been identified to antagonize CDCA-activated FXR at 30 μM in a luciferase reporter gene assay (Shin et al., 2012).

3.4. FXR as target in precision medicine

As emphasized in previous chapters, FXR is a major regulator of metabolic processes and therefore it is plausible that genetic variations within the FXR gene have an impact on disease development or progression. A recent review by Koutsounas et al. summarized the data up to 2014 (Koutsounas et al., 2015).

In the coding region of FXR, several different polymorphisms have been described. Interestingly, two rare nonsynonymous gain-of-function variants have been reported in European-, African-, Chinese-, and Hispanic-Americans in the conserved hinge regions of the FXR gene. They are referred to as FXR*2 and FXR*3, respectively. Additionally, the same study reported a common -1G > T polymorphism in the Kozak sequence of the start codon, referred to as FXR*1B (rs56163822). The prevalence of this polymorphism ranged from 12.1% in Chinese-Americans to 2.5% in European-Americans, with Hispanic-, and African- Americans in between. For FXR*2 and FXR*3, basal and bile acid-activated luciferase-reporter activities were increased, and for FXR*1B lowered when compared to wildtype. However, the reduced transactivation activity of FXR*1B was not due to a changed transcription or translation of FXR. Despite these results, *in vivo* target gene expression data from human livers clearly correlate FXR*1B with reduced target gene expression (Marzolini et al., 2007). The same FXR variant was identified in a different study where reduced translation efficiency was suggested as a mechanism for the lowered luciferase expression (Van Mil et al., 2007). Additionally, this -1G > T polymorphism has been associated with lipid responses to 10 mg daily rosuvastatin treatment for at least four weeks in 385 Chinese hyperlipidemic patients. Baseline lipids were unchanged in patients with the -1G > T polymorphism, however, after rosuvastatin treatment, reductions of 4.4 and 2.6% in LDL cholesterol and total cholesterol, respectively, were observed between the genotype groups. Interestingly, patients homozygous for TT had the strongest LDL cholesterol response to rosuvastatin whereas heterozygotes had only intermediate responses, which were significantly different when compared to wild-type alleles. This effect might be due to the influence of the -1G > T polymorphism on the expression of the efflux transporter ABCG2, that determines the hepatic exposure to rosuvastatin, or might rely on the differences in lipid metabolism or pharmacodynamics of rosuvastatin (Hu et al., 2012). In a more recent study, the effect of the -1G > T polymorphism on the pharmacokinetics of ursodeoxycholic acid was investigated. However, due to the small sample size and lack of homozygous subjects, no clear conclusion could be drawn (Hu et al., 2016).

In an extensive study, 2166 healthy German subjects were genotyped for seven SNPs in the FXR gene and investigated regarding their influence on glucose and lipid metabolism, body fat mass, and liver fat content. All seven analyzed tagging SNPs (rs35735, rs1030454, rs11110415, rs11610264, rs17030285, rs4764980, and rs11110390) covered 100% of common genetic variations with minor allele frequency over 10%. None of the investigated SNPs had an influence on body mass index, percentage of body fat, liver fat content, or insulin secretion and sensitivity. The SNP rs4764980, however, was significantly associated with fasting glycemia and nominally associated with fasting and postglucose load free fatty acid levels. The association with fasting glycemia could be replicated in a meta-analysis. Another SNP, rs11110390, was significantly associated with fasting and postload free fatty acid levels, had, however, no effect on fasting or postload glycemia. Interestingly, these two polymorphisms are intronic and not linked to exonic polymorphisms. The amino acid sequence of FXR is not changed. Therefore, it is likely that they influence the transcription of FXR and not protein functions. All other SNPs investigated in this study were not significantly associated with glucose or free fatty acid concentrations (Heni et al., 2013).

Quantitative trait locus mapping in inbred mice was able to identify the NR1H4 gene as candidate gene for the cholesterol gallstone susceptibility locus Lith7. In Mexican, Chilean and German populations, three frequent haplotypes that accounted for more than 95% of all haplotypes observed were identified. In the Mexican population, the most common haplotype NR1H4_1 was associated with gallstone prevalence. Controversially, in the Chilean population the NR1H4_1 haplotype was associated with a protective effect, although not significant. Then again the NR1H4_1 haplotype in the German population did not show a relationship to gallstone prevalence. This study indicated complex interactions of NR1H4 alleles for the risk of gallstone formation (Kovacs et al., 2008).

It has previously been suggested that genetic variation in FXR leads to higher susceptibility to intrahepatic cholestasis of pregnancy (ICP). ICP presents itself with pruritus and liver impairment and can lead to severe complications in pregnancy. In the study from Van Mil et al., the coding regions and intron/exon boundaries of FXR were sequenced in 92 British ICP cases of mixed ethnicity. Four novel SNPs linked to ICP were identified, -1G > T, M1V, W80R, and M173T. M1V was only detected in one case and W80R could not be detected at all in Caucasians. The -1G > T and M173T variants occurred more frequently, however, only M173T could be connected to ICP (Van Mil et al., 2007).

FXR is an important protective factor in the development of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (UC). Therefore, Attinkara et al. investigated the influence of five FXR variants on IBD. Among the five variants selected were three rare ones, rs3863377, rs56163822 (-1G > T, FXR*1B), and rs7138843, with minor allele frequencies of 4%, 2.2% and 0.9%, respectively. Rs10860603 and rs35724 are common SNPs with minor allele frequencies of 20.5% and 40.8% in Europeans. Two rare SNPs, rs3863377 and rs56163822 were significantly associated with IBD. Rs3863377 is significantly less frequent in IBD cases than in non-IBD controls, suggesting a protective effect of this variant. On the other hand, the variant rs56163822 (-1G > T) is less common in non-IBD controls than in IBD cases, correlating to the reduced FXR activity reported previously and linking this variant to IBD development. For the other three investigated SNPs in this study, no significant differences could be observed. Therefore, the predicted global haplotype patterns were significantly different in IBD patients and non-IBD control, further suggesting an association of FXR variants with IBD and making genetic screening a potential early diagnostic and therapeutic tool for IBD (Attinkara et al., 2012). In another study, seven common tagging SNPs (rs12312471, rs11110390, rs4764980, rs11110395, rs11610264, rs10860603 and rs35739) and two functional SNPs (rs56163822 and rs61755050) in FXR were genotyped in 2355 Dutch IBD patients and 853 healthy controls. However, none of the investigated SNPs were significantly associated with Crohn's disease or UC (Nijmeijer et al., 2011).

Homozygous c.526C > T mutation in FXR prematurely terminates the protein at amino acid 176 in the DNA-binding domain, leading to a loss of FXR function and FXR-related cholestasis with neonatal onset and rapid progression to end-stage liver disease, early onset vitamin K-independent coagulopathy, low-to-normal serum gamma-glutamyl transferase, elevated serum alpha-fetoprotein and undetectable liver BSEP expression (Gomez-Ospina et al., 2016).

Taken together, genetic FXR variants are associated with susceptibility to various metabolic processes, like glucose homeostasis, gallstone formation, ICP and IBD. However, the data available is few and

especially the influence of FXR SNPs on drug treatment needs to be investigated in more detail. In total, there is a striking absence of nonsynonymous SNPs in FXR, suggesting that variations in this highly conserved gene have extensive consequences on the maintenance of tissue and cell functions.

4. The retinoid X receptor (RXR)

The nuclear receptor RXR is expressed in three different isoforms (NR2B1-3) (Auwerx et al., 1999). The genes of these isoforms are located on chromosome 9, 6 and 1 (bands q34.3, 21.3 and q22-q23, respectively) and are differentially expressed in different tissues (Almasan et al., 1994; Mangelsdorf et al., 1992). Interestingly, all RXR isoforms are mostly interchangeable in function and each cell expresses at least one isoform (Evans and Mangelsdorf, 2014).

RXR forms heterodimers with other nuclear receptors, such as LXRα/β, FXR and PPARα/δ/γ but also with the thyroid hormone receptors (TRα/β) and the VDR. Although RXR as heterodimer partner of the thyroid hormone and vitamin D receptor remains silent (RXR ligands cannot activate these non-permissive receptors), RXR ligands can display a variety of biological functions by modulating permissive nuclear receptors, including LXR, FXR and the PPARs (Dawson and Xia, 2012; Evans and Mangelsdorf, 2014). Moreover, RXR is able to act as homodimer (Lefebvre et al., 2010) and to aggregate to homotetramers (Gilardi and Desvergne, 2014). The final expression pattern induced by an RXR ligand may vary depending on the protein abundance of RXR and respective heterodimer partners as well as coregulators in the respective tissue, the affinity of the heterodimer partner to RXR, the allosteric changes induced by the RXR ligand in the LBD and consequently the allosteric interaction with the heterodimer partner or coregulators, the promoter context, the target gene (Gilardi and Desvergne, 2014) and posttranslational modifications of the receptor (Dawson and Xia, 2012).

4.1. The role of RXR in metabolic processes

As common RXR-partnered permissive nuclear receptors, such as LXR, FXR and the PPARs, are involved in the maintenance of metabolic and energy homeostasis, RXR plays a unique role in integrating the action of these nuclear receptors that are regulated by a large number of endogenous low-affinity ligands such as oxysterols (LXR), bile acids (FXR) and fatty acids (PPARs) (Gilardi and Desvergne, 2014) (Evans and Mangelsdorf, 2014).

4.1.1. Influence on lipid metabolism

Ligands of RXR contribute to the control of cellular cholesterol uptake, its efflux and cholesterol storage due to the modulation of permissive heterodimers, of which the best studied are those with PPARs and LXRs (Nagy et al., 2012; Nagy et al., 2013; Roszer et al., 2013). In macrophages, which play an important role in the development of atherosclerosis, important receptors for lipid uptake are the scavenger receptors, especially scavenger receptor class B member 3 (CD36) and the scavenger receptor class A (SR-A) (Chinetti-Gbaguidi and Staels, 2009). RXR agonists were shown to upregulate the expression of the PPARγ-target gene CD36, but to decrease SR-A activity resulting in a moderate oxLDL uptake in macrophages (Argmann et al., 2003; Nishimaki-Mogami et al., 2008). The net effect of RXR activation in macrophages is a decreased cellular cholesteryl ester accumulation. This appears to be mainly due to an increased cellular cholesterol efflux mediated by the PPARγ:LXR:ABCA1 pathway. Several RXR agonists, including 9-cis retinoic acid, PA024, HX630, bexarotene, LG100268 or the natural product honokiol have been shown to promote the expression of the cholesterol efflux mediating ABC transporters, ABCA1 and ABCG1, in different monocyte/macrophage cellular systems (Argmann et al., 2003; Kotani et al., 2010; Lalloyer et al., 2006; Nishimaki-Mogami et al., 2008). In accordance, bexarotene inhibits atherogenesis in APOE2-KI mice and clinical data showed that low RXRα expression in macrophages was more frequently observed in hypertensive and hyperlipidemic patients (Giaginis et al., 2011; Lalloyer et al., 2006). ABCA1 dysfunction or deficiency in the brain was linked to an increased risk for Alzheimer's disease and thus RXR agonists may have potential for the treatment of not only metabolic but also neurodegenerative disorders (Koldamova et al., 2014). However, several RXR agonist were shown to increase plasma triglyceride levels due to transactivating LXR/RXR-target genes implicated in lipogenesis in the liver, like SREBP1c, FAS and SCD-1 (Lalloyer et al., 2006; Lalloyer et al., 2009; Roder et al., 2007). There appear to be, however, considerable differences in inducing lipogenic gene expression between various RXR agonists (Pinaire and Reifel-Miller, 2007; Vedell et al., 2013).

4.1.2. Influence on glucose metabolism

RXRs, as obligate heterodimer partner of permissive nuclear receptors such as the PPARs, the LXRs, and FXR contribute to the regulation of glucose metabolism. Indeed, rexinoids have insulin sensitizing effects and lower hyperglycemia in animal models, although they show differential effects on gene expression of metabolic target genes (Morishita and Kakuta, 2017). Direct actions of rexinoids on insulin secretion have recently been suggested by several studies. In one study, 9-cis retinoic acid was shown to be present in the pancreas at concentrations of about 20 pmol/(g or ml), varying with feeding, fasting and glucose challenges in rodents. Levels of 9-cis retinoic acid were inversely correlated with insulin levels (Kane et al., 2010). Endogenous RXR was also shown to negatively regulate insulin secretion under high glucose conditions in pancreatic cells (Miyazaki et al., 2010). Whether RXR functions in the pancreas as a homodimer or in concert with PPAR, LXR, FXR or other nuclear receptors is not yet known (Brun et al., 2013). 9-cis retinoic acid was not detected at significant levels in other tissues until then and it was even debated whether it is an endogenous ligand (Kane, 2012; Wolf, 2006).

4.1.3. RXR in the inflammatory response

RXRs regulate important functions of monocytes/macrophages, dendritic cells and also T-cells. Thus, this receptor plays a role in the innate as well as in the adaptive immune response (Pino-Lagos et al., 2010; Roszer et al., 2013). Heterodimers of RXR with PPARs and LXRs are the most extensively studied nuclear receptors involved in immune responses with crucial roles in apoptotic cell clearance, neutrophil homeostasis, immune cell proliferation, T-cell differentiation and inflammatory gene repression (Kidani and Bensinger, 2012). Independent of a heterodimer partner, RXRα signaling was shown to control innate inflammatory responses by upregulating chemokine expression in myeloid cells (Nunez et al., 2010). More recently, other RXR heterodimers were identified to be involved in the immune response such as VDR, FXR, nuclear receptor subfamily 4 group A member 2 (Nurr1), nuclear receptor subfamily 4 group A member 1 (Nur77), the PXR, RARs and the TR (Anand et al., 2008; Hamers et al., 2013; Mencarelli et al., 2009; Nagy et al., 2012).

RXRα appears to repress the host antiviral response in mice. During a viral infection, the host suppresses RXRα expression which leads to an optimal expression of interferon regulatory factor 3-dependent type I interferon. Therefore, RXR antagonists might have a potential application to treat viral-infection related diseases (Ma et al., 2014).

4.2. RXR as therapeutic target

A synthetic RXR-selective ligand, the full RXR agonist Bexarotene (Targretin™, LGD1069), is approved to treat advanced stage cutaneous T-cell lymphoma and also has been used off-label to treat breast cancer. The compound has a high affinity for RXRα, β or γ with K_d values of 14 ± 3, 21 ± 4, and 29 ± 7 nM, respectively, and low affinity to the RAR isoforms (K_d > 1000 nM) (Boehm et al., 1994; Farol and Hymes,

2004; Hamann, 2000). However, side effects like elevated triglyceride levels, suppression of the thyroid hormone axis and hypercholesterolemia limit its use (Duvic et al., 2001; Esteva et al., 2003; Pinaire and Reifel-Miller, 2007; Qu and Tang, 2010).

Other rexinoids are tested in preclinical settings for their potential to treat atherosclerosis, insulin resistance, diabetes, obesity, cancer and dementia, amongst others (Dawson and Xia, 2012; Pinaire and Reifel-Miller, 2007; Qu and Tang, 2010). In order to avoid side effects of full retinoid X receptor agonists like hypertriglyceridemia, a current challenge in drug discovery is to identify and characterize selective RXR modulators (SRXRMs) that include hetero- and homodimer-specific RXR agonists and antagonists, ligands that act in a tissue-specific manner or that activate only a subset of genes induced by pan-RXR agonists. SRXRMs may help to achieve the requested pharmacological effect without severe side effects (Pinaire and Reifel-Miller, 2007; Roszer et al., 2013).

4.3. Natural product-derived ligands for RXR

Ligands for RXR (rexinoids) that are natural product-derived, represent a diverse set of molecules. Endogenous rexinoids originate from the vitamin A (retinol) metabolism. Cellular uptake of retinol from the blood stream leads to its conversion into retinoic acid and subsequent transport to the cell nucleus where it acts as transcriptional activator (Maden, 2002). 9-cis retinoic acid (Table 3) is discussed as endogenous RXR ligand. This, however, is controversial, since under normal conditions 9-cis retinoic acid is not detectable in serum. More recently, 9-cis retinoic acid was, however, found to be present in the pancreas regulating insulin secretion (Kane et al., 2010). In an RXRα-dependent reporter gene experiment in CV-1 cells, 9-cis retinoic acid acted as a potent agonist with an EC_{50} of 50 nM (Heyman et al., 1992). 9-cis-13,14-dihydroretinoic acid (Table 3) was the first endogenous ligand described for RXR with a physiological relevance in mammals, displaying an effect starting at a concentration of 100 nM in reporter gene assays in COS-1 cells. It was identified by HPLC-MS and chemical synthesis in mice lacking cellular retinol binding protein (*Rbp1*−/−) displaying memory deficits and thus indicating reduced RXR signaling. 9-cis-13,14-dihydroretinoic acid was found to be reduced in these mice (Ruhl et al., 2015).

Among β-apocarotenoids (eccentric cleavage products from β-carotene), β-apo-13-carotenone (Table 3) was identified as high-affinity RXRα ligand and antagonist (K_i of 8 nM) (Eroglu et al., 2010, 2012). It has been shown that this natural product is able to induce RXR tetramerization that silences this nuclear receptor (Sun et al., 2014). A further cleavage product, β-apo-14′-carotenal (Table 3) was found to repress RXRα, PPARα and PPARγ transactivation and respective biological responses, such as adipogenesis (Ziouzenkova et al., 2007).

Unsaturated fatty acids are dietary-derived ligands for RXR. Starting with the discovery that docosahexaenoic acid (22:6), arachidonic acid (20:4) and oleic acid (18,1) are able to activate an RXRα-responsive reporter gene in HEK293 cells (de Urquiza et al., 2000), additional unsaturated fatty acids were discovered as RXR ligands (Dominguez et al., 2017). Since it would go beyond the scope of this review to list all available data on unsaturated fatty acids we will exemplarily summarize data regarding the above mentioned unsaturated fatty acids in Table 3 (Goldstein et al., 2003; Lengqvist et al., 2004).

The natural product phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) is a metabolite of phytol that originates from chlorophyll metabolism and can be obtained from the diet, such as milk, meat and fish (Kitareewan et al., 1996) (Table 3). It has been shown to transactivate RXRα with an EC_{50} of 3 μM in a luciferase reporter assay and to activate next to RXRα also RXRβ and γ in a Gal4-responsive luciferase assay at 20 μM (Lemotte et al., 1996; Zomer et al., 2000). Moreover, phytanic acid did also act as ligand for PPARα in a Gal4-responsive luciferase assay at 20 μM (Zomer et al., 2000). Dietary sources of phytanic acid, its metabolism and concentration reached in human plasma as well as physiological effects are reviewed by Hellgren (2010).

The isoprenoid methoprene is a juvenile hormone analog used for mosquito control. Its metabolite methoprene acid (Table 3) has been shown to transactivate RXR in a cell-based transactivation model in CV-1 cells with an EC_{50} value of 20 μM and 7 μM, respectively (Harmon et al., 1995). Additionally, methoprene acid has been shown to bind RXRα in a concentration-dependent manner, whereas methoprene was not able to do so (Harmon et al., 1995). Since the ester methoprene can metabolically be activated to methoprene acid, its action on RXR may affect retinoic acid-signaling during development (Schoff and Ankley, 2004).

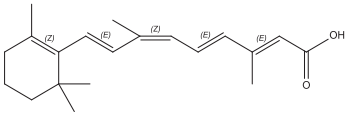
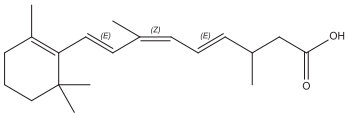
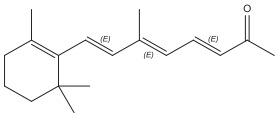
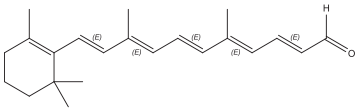
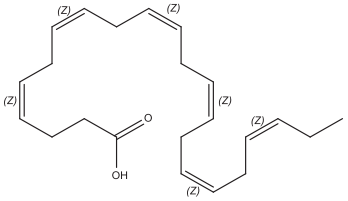
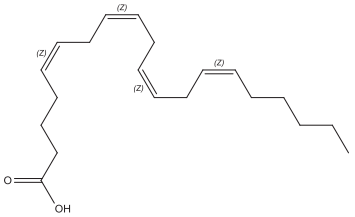
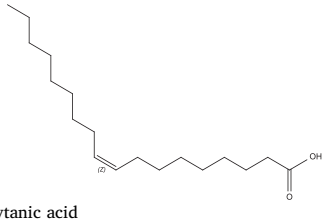
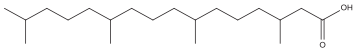
The sesquiterpene lactone bigelovin (Table 3), isolated from the flowers of the plant *Inula hupehensis*, was shown to act as an antagonist of the LXRα/RXRα heterodimer and to enhance PPARγ/RXRα-dependent reporter gene transactivation. Although bigelovin did not transactivate RXRα/RXRα homodimers in cells transfected with RXRα and an RXRE-driven reporter gene, it transactivated RXRα with an EC_{50} of 4.9 μM in a Gal4-responsive luciferase assay in HEK293T cells. Bigelovin was inactive in Gal4-responsive luciferase assays using LBDs of PPARγ, LXRα or FXR (Zhang et al., 2011b). Bigelovin isolated from *Inula helianthus-aquatica*, a traditional medicinal plant used to treat some cancers in China, has been shown to inhibit cell growth of several cancer cell lines such as BEL-7402 (liver cancer), SGC-7901 (gastric cancer), K562 and U937 (leukemia) (Zeng et al., 2009).

The anthraquinones danthron and rhein (Table 3) are natural rexinoids isolated from rhubarb (dahuang), roots and rhizomes of the plant *Rheum palmatum*. Danthron and rhein both antagonize 9-cis retinoic acid-stimulated transactivation of the RXRα-LBD in a Gal4-responsive luciferase assay with IC_{50} values of 0.11 μM and 0.75 μM, respectively. Both compounds appear to antagonize RXRα by stabilizing receptor tetramers. Furthermore, danthron has been shown to enhance insulin sensitivity *in vivo* in danthron-treated dietary-induced obesity mice (Zhang et al., 2011a, 2011d).

The xanthone cochinchinone B (CF31; Table 3) was discovered in a natural product screen and was shown to antagonize 9-cis retinoic acid-stimulated RXRα-dependent reporter gene activation as well as 9-cis retinoic acid-induced transactivation of the RXRα-LBD in a Gal4-responsive luciferase assay. Cochinchinone B displaced [^{3}H]9-cis-RA with an IC_{50} of 9.6 μM from the RXRα-LBD (Wang et al., 2013).

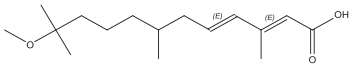
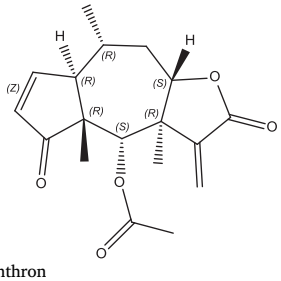
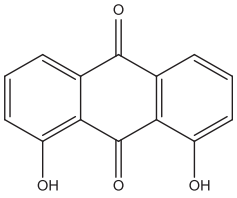
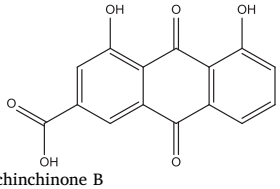
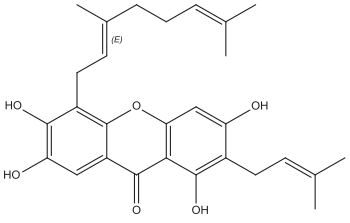
Honokiol (Table 3) is derived from the bark of *Magnolia obovate*, *Magnolia officinalis* or other *Magnolia* species, which are used in traditional Japanese and Chinese medicine (*Hou Po*) (Lee et al., 2007; Rajgopal et al., 2016). It is reported to have a plethora of activities, including anxiolytic, neuroprotective, analgesic, anti-tumorigenic, anti-inflammatory, and antioxidant effects (Fried and Arbiser, 2009; Woodbury et al., 2013). In a HEK293 cell-based luciferase reporter gene assay, honokiol was found to activate human RXRα with an EC_{50} of 11.8 μM as partial agonist. It did, however, not transactivate human RARα−, human LXRα-, mouse PPARγ−, and human PPARβ/δ-dependent luciferase gene expression up to 50 μM. In a yeast two-hybrid assay, honokiol exhibited higher binding activity to RXRα than docosahexaenoic acid (DHA) and phytanic acid, but was less potent than 9-cis retinoic acid (Kotani et al., 2010). In murine RAW264.7 cells, honokiol enhanced mRNA levels of the LXR/RXR target genes ABCA1 and ABCG1 at 20 μM and increased cholesterol efflux from murine peritoneal macrophages at 30 μM that was increased by the endogenous LXR ligand 22(*R*)-hydroxycholesterol synergistically (Kotani et al., 2010). Jung et al. (2010) reported increased ABCA1 mRNA and protein level in the U251-MG glioma cell line in response to honokiol (5–20 μM), which occurred RXR-dependently. They also showed increased ABCA1, ABCG1 and APOE mRNA and protein level in human THP-1 macrophages after honokiol (10 μM) treatment. Also in rat primary neurons and astrocytes ABCA1 was increased. A follow-up study of Kotani et al. (2012) focused on the question which RXR-heterodimers can be activated by honokiol. Thus, they studied selected PPARγ, LXR,

Table 3
Natural products modulating RXR activity.

Natural product	Test system	Potency/efficacy	Reference
9-cis retinoic acid Discussed as endogenous agonist 	Transactivation activity in a luciferase reporter gene assay (RXRα; CRBPII promoter) Ligand binding assay with 9-cis-[^{3}H]RA to baculovirus-derived RXRα	EC_{50} (insect S2 cells) 10 nM EC_{50} (CV-1 cells) 50 nM K_D 11.7 nM	(Heyman et al., 1992)
9-cis-13,14-dihydroretinoic acid Endogenous agonist 	Binding affinity by fluorescence quenching analysis (RXRα-LBD) Crystal structure Mammalian one-hybrid assay	K_D 90 ± 20 nM (*versus* 20 ± 10 nM for 9-cis-RA) together with hRXRα-LBD Transactivation activity > 100 nM	(Ruhl et al., 2015)
β-apo-13-carotenone 	Transactivation activity in a luciferase reporter gene assay (RXRα; CRBPII promoter) Competitive binding assay with 9-cis-[^{3}H]RA to RXRα Mammalian one-hybrid assay Gel filtration analysis	Concentration-dependent (1 nM–1 μM) shift of the concentration-response curve of 9-cis-RA K_i: 8 nM No response, neither in the absence nor presence of 9-cis-RA Induction of tetramerization of the RXRα-LBD	(Eroglu et al., 2010; Eroglu et al., 2012; Sun et al., 2014)
β-apo-14′-carotenal 	Mammalian one-hybrid assay Functional studies	At 5 μM inhibition of RXRα activation in the presence of the RXR agonist LG100364 (at 10 μM also antagonistic effects on PPARα and PPARγ) Inhibition of adipogenesis in 3T3-L1 preadipocytes in the absence or presence of a PPARγ agonist	(Ziouzenkova et al., 2007)
Docosahexaenoic acid (DHA)  Arachidonic acid (AA)  Oleic acid (OA) 	Transactivation activity in luciferase reporter gene assays (hRXRα; APOA1 promoter) Two-hybrid reporter assays (mRXRα, SRC-1) Competitive binding assay with 9-cis-[^{3}H]RA to mouse RXRγ Mass spectrometric analysis of RXRα-LBD Ligand complexes	EC_{50} (DHA) 50–100 μM EC_{50} (AA) > 200 μM EC_{50} (OA) > 200 μM DHA was active also on RXRβ and RXRγ at 150 μM reaching about 40–45% of the level of 0.1 μM of 9-cis RA When fatty acids had not been prediluted in plastic tubes: EC_{50} 5–10 μM EC_{50} (DHA) 66 μM EC_{50} (AA) 63 μM EC_{50} (OA) 82 μM K_i (DHA) 2.5 μM K_i (AA) 6.5 μM K_i (OA) 5.1 μM DHA, AA, and OA formed RXRα-LBD complexes, besides other PUFAs	(de Urquiza et al., 2000; Goldstein et al., 2003; Lengqvist et al., 2004)
Phytanic acid 	Transactivation activity in luciferase reporter gene assays (RXRα; CRBPII promoter) in Schneider SL-3 cells Competitive binding assay with 9-cis-[^{3}H]RA to RXRα Competitive binding assay with 9-cis-[^{3}H]RA to RXRα, RXRβ, RXRγ Mammalian one-hybrid assay	EC_{50} 3 μM (*versus* no activity against RARα) IC_{50} 2.3 μM (*versus* no activity against RARα) K_i value (RXRα): 4.4 μM K_i value (RXRβ): 4.1 μM K_i value (RXRγ): 3.6 μM At 20 μM binding to RXRα-LBD, RXRβ-LBD, RXRγ-LBD, but also PPARα-LBD	(Kitareewan et al., 1996; Lemotte et al., 1996; Zomer et al., 2000)

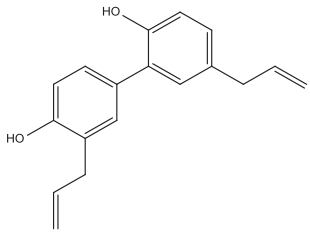
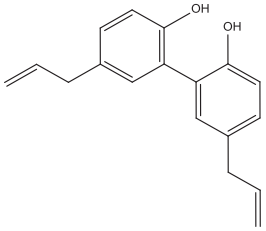
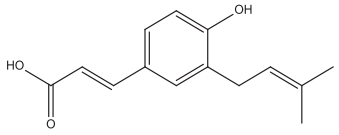
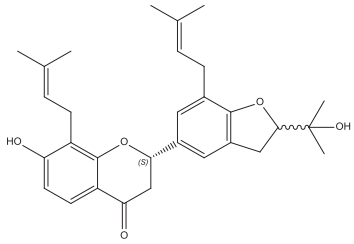
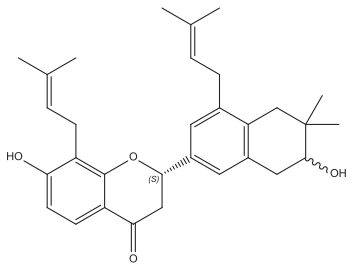
(*continued on next page*)

Table 3 (*continued*)

Natural product	Test system	Potency/efficacy	Reference
Methoprene acid 	Transactivation activity in luciferase reporter gene assays (mRXRα, mRXRβ, mRXRγ; CRBPII promoter)	Concentration-dependent (1–100 μM) activation of mRXRα, mRXRβ, mRXRγ EC_{50} 2 μM (Schneider cells) EC_{50} 20 μM (CV-1 cells) E_{max} n.d., however with a very weak response towards mRXRβ	(Harmon et al., 1995; Schoff and Ankley, 2004)
	(hRXRα, CRBPII promoter)	EC_{50} 7 μM (CV-1 cells)	
	Competitive binding assay with 9-cis-[^{3}H]RA to RXRα	Concentration-dependent (1-100 μM) binding to RXRα	
	Mammalian one-hybrid assay	Activation of GAL4-hRXRα (concentartion not given)	
Bigelovin 	Mammalian one-hybrid assay	EC_{50} 4.9 μM with no activity against PPARγ, FXR, LXRα	(Zhang et al., 2011b)
	SPR technology-based assay	Binding to RXRαLBD: K_D 7.7 μM With no binding affinities to PPARγ, FXR, LXRα	
	ITC-technology-based assay	Binding to RXRαLBD: K_D 8.7 μM	
	Transactivation activity in luciferase reporter gene assays	Repressive effect on RXRE (RXRα:RXRα) Enhanced transactivation on PPRE (RXRα: PPARγ) Repressive effect on LXRE (RXRα: LXRα) No effect on FXRE (RXRα:FXR)	
	Crystal structure	of bigelovin-bound RXRα-LBD-SRC1	
Danthron 	SPR technology-based assay	Binding to RXRα-LBD: K_D 6.2 μM	(Zhang et al., 2011d)
	ITC-technology-based assay	Binding to RXRα-LBD: K_D 7.5 μM	
	Mammalian one-hybrid assay	Inhibition of 9-cis-retinoic acid-induced RXRα transactivation, IC_{50} 0.11 μM with no activity against PPARγ, FXR, LXRα	
	Transactivation activity in luciferase reporter gene assays	Repression of RXRα homodimers and PPARγ, FXR, LXRα heterodimers	
	Crystal structure	of danthron-bound RXRα-LBD: two ligands bound to one tetrameric RXRα-LBD	
Rhein 	Mammalian one-hybrid assay	Inhibition of 9-cis-retinoic acid-induced RXRα transactivation, IC_{50} 0.75 μM with no activity against PPARγ, FXR, LXRα	(Zhang et al., 2011a)
	Transactivation activity in luciferase reporter gene assays	Repression of RXRα homodimers and PPARγ, FXR, LXRα heterodimers	
	Cocrystallization and structural analysis	RXRα-LBD-rhein-SMRT complex	
Cochinchinone B 	Transactivation activity in CAT reporter assays (RXRα; TREpal promoter)	Concentration-dependent (1–20 μM) inhibition of 9-cis-RA-induced TREpal-reporter activity	(Wang et al., 2013)
	Mammalian one-hybrid assay	Concentration-dependent (1–10 μM) inhibition of 9-cis-RA- or CD3254–induced reporter activity	
	Competitive binding assay with 9-cis-[3H]RA to RXRαLBD	IC_{50} of 9.6 μM	

(*continued on next page*)

Table 3 (*continued*)

Natural product	Test system	Potency/efficacy	Reference
Honokiol 	Transactivation activity in luciferase reporter gene assays (hRXRα; CRBPII promoter)	EC_{50} 11.8 μM (partial agonist compared to Bexaroten; E_{max} n.d.) No activity against hRARα, hLXRα, mPPARγ, hPPARδ (up to 50 μM)	(Atanasov et al., 2013; Jung et al., 2010; Kotani et al., 2012; Kotani et al., 2010)
	Target gene expression studies (mRNA)	RAW264.7: ABCA1, ABCG1 HLE: ANGPTL-4, CYP24A1 3T3-L1: Adiponectin, GLUT4, aP2, ABCA1, ABCG1, APOE Caco-2: CYP24A1, D9k, TRPV6 U251-MG: ABCA1 THP-1: ACBCA1, ABCG1; APOE Rat primary neurons: ABCA1 Rat primary astrocytes: ABCA1, APOE (Main concentration used: 10 or 20 μM)	
	Target gene expression (protein)	RAW264.7: ABCA1 HLE: ANGPTL-4, ABCA1 HEK293: CYP24A1 U251-MG: ABCA1 THP-1: ACBCA1, ABCG1; APOE Rat primary neurons: ABCA1 Rat primary astrocytes: ABCA1, APOE (Main concentration used: 10 or 20 μM)	
	Functional studies	Increased cholesterol efflux from peritoneal macrophages at 30 μM Increased cellular glucose uptake in mature 3T3-L1 adipocytes (1–10 μM) No adipogenicity in 3T3-L1 preadipocytes up to 10 μM	
Magnolol 	Binding activity in a mammalian one–hybrid assay	EC_{50} 10.4 μM for RXRα (*versus* 17.7 μM for PPARγ)	(Zhang et al., 2011c)
	Surface plasmin resonance (SPR) analysis	K_D 45.7 μM for RXRα-LBD (*versus* 1.67 μM for PPARγ-LBD)	
	Transactivation activity in luciferase reporter gene assays	No activity at 0.1–20 μM *via* RXRα on RXRE Dose-dependent transactivation (1–20 μM) *via* RXRα and PPARγ on PPRE	
	Crystal structure analysis	of RXRα-LBD-magnolol-SRC-1 and PPARγ-LBD-magnolol showed one molecule binding to RXRα and two molecules binding to PPARγ	
Drupanin 	Transactivation activity in luciferase reporter gene assays (hRXRα; CRBPII promoter)	EC_{50} 4.8 μM; efficacy rate of approximately 62.5% of bexarotene	(Nakashima et al., 2014)
	Binding activity by measuring ligand–dependent coactivator recruitment	EC_{50} (RXRα) 2.1 μM EC_{50} (RXRβ) 4.6 μM EC_{50} (RXRγ) 7.0 μM EC_{50} (PPARα) 39.0 μM EC_{50} (PPARγ) 14.6 μM	
	Functional studies	At 25 μM induction of adipogenesis in 3T3-L1 cells	
Prenylated flavanones 1 	Transactivation activity in luciferase reporter gene assays (hRXRα; CRBPII promoter)	EC_{50} 0.77 μM (compound 1) EC_{50} 0,78 μM (compound 2)	(Inoue et al., 2014)
	Binding activity by measuring ligand–dependent coactivator recruitment	Both compounds bind to RXRα, RXRβ and RXRγ	
	Target gene expression studies (mRNA)	Tested both at 10 μM for ABCA1, ANGPTL-4, CYP26A1, CYP14A1, SREBP-1, FAS, APOD, APOE, LPL, CPT1A, HMOX-1, FABP3 in various cell types	
	Functional studies	At 10 μM induction of adipogenese in 3T3-L1 cells	
2 			

VDR target genes in various cell lines (HLE hepatoma, HEK293, 3T3-L1 adipocytes, Caco-2). In most models, honokiol (20 μM) acted as "conditional agonist", showing synergistic activity in the presence of a liganded heterodimer partner but being inactive or weakly active when applied alone. Furthermore, honokiol was shown to increase basal glucose uptake in differentiated 3T3-L1 adipocytes without inducing adipogenicity in 3T3-L1 preadipocytes up to 10 μM (Atanasov et al., 2013). By using NMR spectroscopy and modeling as well as cellular assays, Scheepstra et al. (2014) proposed that honokiol displays a specific binding mode, binding to the ligand-binding pocket side of the AF2 but also to the coactivator side of the AF2.

The structurally closely related magnolol (Table 3) is a more potent PPARγ agonist in comparison to honokiol and also binds RXRα. In Gal4-responsive luciferase assays, magnolol activated RXRα-dependent gene expression concentration-dependently with an EC_{50} value of 10.4 μM, and PPARγ-dependent gene expression with an EC_{50} value of 17.7 μM in HEK293T cells (Zhang et al., 2011c). A lower EC_{50} value of 1.62 μM was found for magnolol in HEK293 cells transfected with a PPARγ expression plasmid and a PPRE-driven luciferase reporter gene (Fakhrudin et al., 2010).

Another naturally occurring rexinoid is drupanin (Table 3), a constituent of Brazilian green propolis (BGP). BGP is used in traditional medicine and produced by honey bees (*Apis mellifera*) from plant exudates of the asteraceous plant *Baccharis dracunculifolia*. Drupanin activated RXRα-dependent gene expression in a luciferase reporter gene assay in HEK293 cells with an EC_{50} value of 4.8 μM, but did not transactivate RARα, LXRα or VDR in this assay. Furthermore, drupanin was not selective for the different RXR isoforms and was able to recruit SRC-1 in a nuclear receptor cofactor recruitment assay *in vitro* to RXRα, β and γ (EC_{50} values of 2.1 μM for RXRα, 4.6 μM for RXRβ and 7.0 μM for RXRγ). Drupanin was shown to also moderately bind to PPARγ in a nuclear receptor cofactor recruitment assay *in vitro* and to recruite CREB (cAMP response element-binding protein)-binding protein with an EC_{50} of 14.6 μM. Drupanin induced adipogenesis in mouse 3T3-L1 fibroblasts and elevated mRNA levels of the PPARγ target gene adipocyte fatty acid-binding protein-2 (*aP2*) (Nakashima et al., 2014).

In the same year, two prenylated flavanones (Table 3) isolated from *Sophora tonkinensis*, a traditional Chinese plant, were characterized as rexinoids (Inoue et al., 2014). Using a luciferase reporter gene assay in HEK293 cells transfected with human RXRα, the authors found EC_{50} values for both structurally closely related compounds in the range of 0.8 μM. In a nuclear receptor cofactor recruitment assay, both compounds bound *in vitro* to RXRα, β and γ. Using RAW264.7 murine macrophages, HLE human hepatoma cells and C2C12 myotubes, the authors characterized both compounds with respect to their gene expression profile compared to bexarotene, concluding that these rexinoids have properties different from bexarotene.

4.4. RXR as target in precision medicine

Regulation of metabolic homeostasis by RXR heterodimers is very complex and involves the response of ligands derived from cholesterol, fatty acids and glucose. Besides that, together with LXR and the PPARs, RXR is involved in the regulation of inflammatory responses (Huang and Glass, 2010). Therefore, RXR has been considered to be an attractive target for the treatment of the metabolic syndrome, type 2 diabetes and cardiovascular diseases such as atherosclerosis (Bensinger and Tontonoz, 2008; Shulman and Mangelsdorf, 2005).

Several RXR polymorphisms have been identified to be linked to metabolic dysfunctions. In a study of 2008, a polymorphism of the RXRβ isoform (c.51C < T, rs2076310) was linked to higher body mass and gallstone risk, although functional consequences of this SNP are not yet confirmed (Chang et al., 2008).

The RXRγ gene is located on chromosome 1q21-23, a region associated with familial combined hyperlipidemia (FCHL), the most common form of hereditary hyperlipidemia (Nohara et al., 2007). Variations in the RXRγ gene are also linked to elevated triglyceride levels and high LDL cholesterol levels (Pei et al., 2000).

A polymorphism of RXRγ (p.Gly14Ser) was reported to be linked with hyperlipidemia and other RXR variants have been linked to high triglyceride and free fatty acid levels in type 2 diabetes. Nohara et al. found that the RXRγ Ser14 variant is significantly more frequent in patients with FCHL than in the general population or than with other forms of hyperlipidemia. Carriers of this gene variant have higher triglyceride levels, lower HDL cholesterol and lower apolipoprotein A2 levels and a higher coronary stenosis index than carriers of the wild-type allele. This may be the reason for the contribution of this RXRγ gene variant to FCHL (Nohara et al., 2007; Nohara et al., 2009).

Several other SNPs (SNP6, SNP11 and SNP13 [rs10918169]) in the RXRγ gene have been described and associated with type 2 diabetes, higher triglyceride levels and higher free fatty acid levels in case-control studies (Hasstedt et al., 2008; Wang et al., 2002). Furthermore, another SNP (rs3818569) in the RXRγ gene has been associated with increased risk for the development of diabetic retinopathy in a Taiwanese population. However, functional studies need to be performed (Hsieh et al., 2011).

The association of combined polymorphisms of the RXRα and PPARγ genes on metabolic risk has been shown in a case-control study in a Chinese Han population with moderate sample size. Several SNPs of RXRα were found in this study (rs4240711GG, rs4842194 and rs3132291) that may decrease the risk of metabolic syndrome whereas variants of the PPARγ gene (rs2920502CG) may be associated with an increased risk of metabolic syndrome (Shi et al., 2012). Another study by Zhao et al. used a computer-based algorithm to overcome case-study limitations using a back-error propagation artificial neural network analysis, a computer-based method to analyze complex patterns. In concordance with the previous study, they observed a combined effect of RXRα and PPARγ gene variants on metabolic syndrome risk factors in a Chinese Han population (Zhao et al., 2014b).

In summary, gene variants of RXR in different populations are associated with variations in metabolic dysfunctions in different populations and target genes of RXR can be found in susceptibility loci for metabolic syndrome. However, studies on RXR gene variants are few.

5. Conclusion and outlook

Metabolic syndrome-related diseases, such as obesity and diabetes, have alarming prevalence worldwide and are therefore an important health concern (Levesque and Lamarche, 2008). Treatment options for patients suffering from such disorders have to be improved to combat this development.

The here reviewed nuclear receptors are key regulators of energy homeostasis and inflammation. They act as transcription factors, regulating a plethora of respective target genes and thus are potential targets to treat lipid and glucose metabolism-related diseases as well as inflammation.

Natural products can either act as sources for new drugs on their own or as lead structures for drug discovery (Newman and Cragg, 2016). None of the natural products mentioned in this review are in clinical studies, but valuable pharmacological data are already available. To yield commercially relevant products, patentability is a crucial factor, which is often held against natural product research. However, improving the properties of promising natural products by chemical modification can overcome this hurdle. Interestingly, several of the mentioned natural products are food constituents, like taurine, quercetin, sesame oil, naringenin, xanthohumol, soy protein, phytanic acid, and oleanolic acid amongst others, and are therefore potential candidates for dietary interventions (Hernandez-Rodas et al., 2015). Moreover, nutrigenomics and precision nutrition is an emerging field, taking into account the genetic background and metabolic profile of patients and making dietary nuclear receptor ligands an interesting research field (Wang and Hu, 2018). One advantage of natural products, in

particular plant extracts, as opposed to synthetic compounds is that they contain a variety of constituents that may complement each other and might therefore account for their broad spectrum efficacy. Moreover, in the context of nuclear receptors, some pure compounds might have the advantage to act – as their endogenous counterparts – as low affinity ligands and/or partial agonists as exemplified in this review. Thus, they might be an interesting source for the discovery of SNuRMs or act as part of the daily diet or phytopharmaceuticals as modulators of energy homeostasis and inflammation. It also has to be considered that, although several natural products show their effects on nuclear receptors in the mid to high μM range, these concentrations might be reachable locally e.g. in the gut after oral administration.

So far there are multiple studies showing that genetic variations, such as SNPs, in individual nuclear receptor genes are associated with disease risks, thereby allowing a personalized approach to the treatment of these diseases.

However, detailed and broad characterizations of the gene variants of nuclear receptors are needed together with association studies to link certain gene variants with therapeutic success of specific medications and drug interactions.

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