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• Review

# Natural modulators of liver X receptors

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**ABSTRACT:** Nuclear receptor transcription factors are ligand-activated proteins that control various biological events from cell growth and development to lipid metabolism, and energy and glucose homeostasis. Nuclear receptors are important drug targets for metabolic diseases. Liver X receptors (LXRs) are nuclear receptor transcription factors that play essential roles in regulation of cholesterol, triglyceride, fatty acid, and glucose homeostasis. LXR-deficient mice have shown the association of LXR-signaling pathway dysfunction with several human pathologies including atherosclerosis, hyperlipidemia, Alzheimer's disease and cancer. Thus, LXRs are promising pharmacological targets for these diseases. Synthetic LXR agonists may lower cholesterol, but increase triglyceride and induce fatty liver. The naturally occurring LXR ligands, with moderate activity, may serve as nutraceuticals for prevention or treatment of the disorders, while minimizing potential side effects. In this review, recent advances in natural LXR modulators are summarized including agonist, antagonist and the modulator of LXR pathway.
**KEYWORDS:** Liver X receptors; agonist; antagonist; atherosclerosis; steatosis; hyperlipidemia; hypercholesterolemia; hypertriglyceridemia; nutraceuticals; reviews

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## 1 Introduction

Liver X receptor (LXR) is a member of the nuclear receptor transcription factor superfamily. Two isoforms of LXR have been identified as LXRα (NR1H3) and LXRβ (NR1H2)[1,2], which form heterodimers with retinoid X receptor (RXR)[3]. LXR activity could be modulated either by LXR agonists or antagonists. After activation, LXR binds to LXR response element in the promoter region of the LXR target genes to regulate their expression. These genes (including ATP-binding cassette (ABC) transporter isoforms A1 (ABCA1) and G1 (ABCG1), fatty acid synthase (FAS), lipoprotein lipase, sterol regulatory element-binding protein-1c (SREBP-1c), apolipoprotein E (ApoE) cholesteryl ester transfer protein, and carbohydrate regulatory element-binding protein) are involved in cholesterol, fatty acid, lipid and glucose metabolism[4].

LXRs were initially isolated from human liver. Their physiological functions are associated with cholesterol homeostasis[5], and their ligands have been identified as oxidized derivatives of cholesterol. LXRα expression is restricted to tissues such as liver, small intestine, kidney, spleen and adipose tissue. It plays an important role in lipid metabolism in those locations. However, LXRβ is expressed in almost all tissues and organs[6] (also see www.nursa.org).

LXRs are the important regulators of cholesterol, triglyceride, fatty acids, and glucose homeostasis[7,8]. Deficiency of LXRs are linked to various diseases including atherosclerosis, hyperlipidemia, Alzheimer's disease (AD) and cancer in animal models. Thus, LXRs are promising pharmacological targets[7,8]. The present review focuses on the natural modulators of LXR signaling and their potential use in therapies for various diseases.

## 2 Structure and function

LXRs contain four domains: (1) an amino-terminal activation

domain, recruiting ligand-independent co-activators; (2) a DNA-binding domain containing two zinc fingers; (3) a hinge domain, binding co-repressors in the absence of ligand and a multi-functional carboxy-terminal domain, containing a hydrophobic ligand-binding domain (LBD); (4) a transactivation domain required for dimerization and recruiting co-activators[8,9].

LXRs are acetylated at residues K432 in LXRα and K433 in LXRβ in the absence of ligand[10], and bind with RXR to their LXR response element of target gene promoters. The LXR/RXR heterodimer interacts with co-repressors such as nuclear receptor co-repressor or silencing mediator for retinoic acid and thyroid hormone receptor (SMRT)[11] to block transcription by recruitment of histone deacetylase[12]. The binding of ligands to LXR leads to modifications of the carboxyterminal domain that results in release of the co-repressors and initiates gene expression.

## 3 Physiological functions of LXRs

LXRs were discovered as regulators of cholesterol homeostasis[13]. Subsequently, other functions of LXRs were revealed, which include: (1) lipid metabolism including fatty acids, triglyceride and cholesterol homeostasis[14]; (2) glucose homeostasis[15]; (3) steroidogenesis; (4) immunity and inflammation[9]. Analysis of LXR knockout mice has shown that the lack of both LXR isoforms results in the pathogenesis of some diseases such as dyslipidemia, diabetes, atherosclerosis, obesity, cancer, Cushing syndrome and AD[16-23]. Additionally, LXRα$^{-/-}$ and LXRβ$^{-/-}$ mice show reduced fertility in both males[24-26] and females[27-29]. Hence, LXRs are thought to be promising pharmacological targets.

### 3.1 LXR and atherosclerosis

LXRs may interfere with atherosclerosis through several different agonist-dependent pathways. Activation of LXRs decreases intestinal cholesterol absorption, and promotes reverse-cholesterol transportation by directly activating genes that govern cellular cholesterol export[30]. LXR agonists reduce atherosclerotic lesions in *LDLR*-deficient mice[31]. LXRs are also involved in the physiology of macrophages. They inhibit the action on pro-inflammatory genes that recruit negative coregulatory proteins to nuclear factor-κB, and stimulate the expression of ABC transporters involved in cholesterol efflux[32]. This could inhibit transformation of the macrophages into foam cells. Selective LXR agonist WAY-252623 has been shown to reduce the progression of lesions in the mouse LDLR$^{-/-}$ atherosclerosis model[31]. These data demonstrate that activation of LXR could slow the progress of atherosclerosis by its actions in the intestine and on macrophage cells.

### 3.2 LXR and diabetes

Type 2 diabetes is characterized by high-blood glucose and insulin resistance. LXR agonist treatments improved glucose tolerance in diet-induced diabetic models[33,34]. LXR activation also promotes triglyceride accumulation in skeletal muscle cells, probably via the induction of the expression of lipogenic enzymes[34], indicating that LXRs are involved in glucose metabolism and could be potential targets for treatment of type 2 diabetes.

### 3.3 LXR and Alzheimer's disease

AD is a neurodegenerative disease characterized by a progressive cognitive decline with inflammation of the brain. Activation of LXR results in a decrease in the neuroinflammatory response. A synthetic LXR ligand, T0901317, significantly increases ABCA1 expression and inhibits the production of amyloid-β (Aβ) peptide in neurons, suggesting that ABCA1 plays a protective role in AD progression[35]. Treatment with an LXR agonist also significantly decreased Aβ-peptide accumulation[36] and increased memory in APP23 AD model[37]. These data indicate that LXRs may be potential pharmacological targets for the treatment of AD and other neurological diseases caused by unbalance of cholesterol homeostasis[38].

### 3.4 LXR and cancer

LXR agonists have been reported to exert effects on hormone-dependent cancers such as prostate cancer and breast cancer[39]. Activation of LXR significantly reduces cell proliferation by suppressing genes that regulate the cell cycle and estrogen receptor α; conversely it increases the expression of tumor suppressor p53. The synthetic LXR ligand, T0901317, inhibits the proliferation of several cancer cell lines and induces apoptosis of the prostate cancer cell line LNCaP[40,41]. Additionally, oral administration of T0901317 slows the growth of prostate tumor LNCaP cell xenograft in athymic mice[42]. These data suggest that enhancement of LXR signaling may be beneficial to the treatment of hormone-dependent cancer and further indicate the potential use of LXR agonists as pharmacological agents in cancer prevention[43].

## 4 Natural modulators of LXRs

As LXRα and LXRβ are associated with various diseases, LXRs provide promising pharmacological targets. LXR ligands include agonists that induce the transcriptional activity of LXR and antagonists that block their activities on target genes. Synthetic LXR agonists such as T0901317 and GW3965 are effective for treatment of atherosclerosis, diabetes, inflammation, cancers, and AD in mice[17-21]. However, so far all efforts to develop safe and effective LXR agonists have failed because of adverse side effects[7,8]. Thus, naturally occurring compounds that have LXR-modulating activity make excellent candidates for development of therapeutic or nutraceutic agents.

### 4.1 Endogenous agonist ligands

Oxysterols were found to be the endogenous ligands of LXRs

in mammals[5]. Oxysterols include 22(R)-hydroxycholesterol, 20(S)-hydroxycholesterol, 24(S)-hydroxycholesterol, 24(S),25-epoxycholesterol, 25-hydroxycholesterol and 27-hydroxycholesterol[44]. These oxysterols have been reported to activate both LXRα and LXRβ[5,45-49]. Other cholesterol-derived molecules, such as follicular fluid meiosis-activating sterol, may also activate LXRα[50]. A cholesterol precursor desmosterol also activates LXR[51]. Molecules derived from the bile acid pathway such as 6α-hydroxylated bile acids have been proposed as putative ligands, selectively inducing transcriptional activity of LXRα[52].

A recent study has shown that, similar to T0901317, 22(S)-hydroxycholesterol fits into the ligand-binding domain of LXR, but 22(S)-hydroxycholesterol affects LXR-regulated gene expression differently in various cell types[53]. Treatment with 22(S)-hydroxycholesterol resulted in reduction of lipogenesis and lipid accumulation in myotubes and hepatocytes, indicating that 22(S)-hydroxycholesterol may reduce lipid accumulation in non-adipose tissue and has potential to be used in the treatment of type 2 diabetes. It should be noted that these endogenous agonists are also exogenous ligands, because they can be obtained from dietary sources, making them nutraceuticals (Table 1).

### 4.2 Endogenous antagonist ligands

Recently, several endogenous LXR antagonists have been reported (Table 1). Found both endogenously and in a number of foods, 5α,6α-epoxycholesterol (5,6-EC) was the first documented dietary LXR ligand with antagonist activity, and has been demonstrated to be one of the most potent natural LXRα ligands. In an LXR-cofactor interaction assay, 5,6-EC bound directly to LXR-LBD and disrupted the recruitment of a number of cofactors to both LXRα and LXRβ. Further, 5,6-EC acted as an antagonist to LXR-mediated gene expression, indicating that 5,6-EC is an LXR modulator that may play a role in the pathogenesis of atherosclerosis by interfering with the agonistic action of endogenous LXR ligands[54,55]. It has also been reported that 7-cetocholesterol-3-sulfate is an LXR antagonist[55].

Polyunsaturated fatty acids (PUFAs), especially arachidonic acid, have been identified as natural competitive antagonists of LXRs, and bind directly with LBD of both LXRα[56] and LXRβ[57]. PUFAs regulate the expression of hepatic fatty acid elongase 5[60], block the transcription of SREBP-1c and mediate a negative feedback regulation of their own synthesis via repression of LXRα. However, to date, there are no *in vivo* studies demonstrating that PUFAs are antagonists of LXRs.

It has recently been shown that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), one of the major metabolites of arachidonic acid, can act as an antagonist to the formation of LXR/RXR dimers and block the activation of LXR agonist T0901317 on Aβ clearance. $PGF_{2\alpha}$ works by inhibiting LXR target gene ApoE expression, and accelerating inflammatory response to Aβ in microglia[58]. This finding demonstrates a potential association of $PGF_{2\alpha}$ with AD progression, and further suggests that inhibition of $PGF_{2\alpha}$ biosynthesis might be a useful therapeutic strategy for patients with AD. Small heterodimer partner interacting leucine zipper protein (SMILE) is a nuclear co-repressor of LXRα. Ursodeoxycholic acid, one of the secondary bile acids, inhibits LXRα-induced lipogenic gene expression by increasing SMILE promoter activity and reduces SREBP-1c, FAS and ACC protein levels. Knockdown of endogenous SMILE gene expression significantly reverses ursodeoxycholic acid-mediated reduction of SREBP-1c, FAS, and acetyl-CoA carboxylase protein levels[59]. This demonstrates that ursodeoxycholic

**Table 1** Endogenous modulator of LXR

| Component | Effects on LXR | Ref. |
|---|---|---|
| 20(S)-Hydroxycholesterol | Activation of LXRα and β | [46] |
| 22(R)-Hydroxycholesterol | Activation of LXRα and β | [47] |
| 24S-Hydroxycholesterol | Activation of LXRα and β | [48] |
| 24(S),25-Epoxycholesterol | Activation of LXRα and β | [5,45,49] |
| 25-Hydroxycholesterol | Activation of LXRα and β | [5,45,49] |
| 27-Hydroxycholesterol | Activation of LXRα and β | [5,45,49] |
| 6α-Hydroxylated bile acids | Selective activation of LXRα | [52] |
| 5α,6α-Epoxycholesterol | Antagonist of LXRα and β | [54,55] |
| 7-Cetocholesterol-3-sulfate | Antagonist of LXRα and β | [55] |
| Polyunsaturated fatty acids, arachidonic acid | Antagonist of LXRα and β | [56,57] |
| Prostaglandin $F_{2\alpha}$ | LXR/RXR heterodimer antagonism | [58] |
| Ursodeoxycholic acid | Inhibits LXRα activity | [59] |

LXR: liver X receptor; RXR: retinoid X receptor.

acid is a negative regulator of LXR signaling via the activation of SMILE gene expression.

Endogenous antagonists have been considered as the negative regulators of cholesterol. However, there is no evidence that these elements are harmful to health. The physiological functions of the ligands need to be further studied.

### 4.3 Agonist ligands from plants and fungi

Recently, various compounds purified from plants or fungi have been shown to modulate the activity of LXR (Table 2). These naturally occurring compounds have potential therapeutic effects, which might overcome some side effects, such as hypertriglyceridemia. Study of these compounds may develop novel therapies for diseases.

Naturally occurring cholesterol analogues such as sterols and stanols (phytosterols/phytostanols), from the 4-desmethyl family, have been found to reduce serum low-density lipoprotein (LDL)-cholesterol level and to activate both LXRα and LXRβ, and to increase expression of ABCA1 in Caco-2 cells[61]. Stanols and sterols also increase intestinal ABCA1 expression and decrease cholesterol absorption, suggesting that LXR is a target for dietary regulation of intestinal cholesterol metabolism[62]. However, a recent study has shown that dietary plant sterols and stanols inhibit cholesterol absorption within the intestinal lumen, which is independent of LXR[63].

Diterpenes are natural steroids, widely distributed in plants and insects. Stimulation of macrophages with acanthoic acid-related diterpenes induces LXR target gene expression and cholesterol efflux to similar levels observed with synthetic agonists[64]. Using a scintillation proximity assay, acanthoic acid, polycarpol, and gorgostane derivatives selectively activate LXRα in HEK293 cells[65].

Fucosterol, a sterol abundant in marine algae, has hypocholesterolemic effect and increases plasma high-density lipoprotein (HDL) activity. Fucosterol stimulates the transcriptional activity of both LXRα and LXRβ and activates co-activator recruitment in a dose-dependent manner[66]. Further, it induces the transcriptional activation of ABCA1, ABCG1, and ApoE and increases the efflux of cholesterol without induction of cellular triglyceride accumulation[66].

YT-32 ((22E)-ergost-22-ene-1α,3β-diol), derived from tergosterol and brassicasterol, directly binds to LXRα and LXRβ and induces the interaction of LXRα with cofactors. Unlike synthetic LXR agonist T0901317, YT-32 inhibits intestinal cholesterol absorption without increasing plasma triglyceride levels. Thus, YT-32 selectively modulates intestinal cholesterol metabolism[67].

A few natural LXR ligands have been purified from herbal medicines. Gynosaponin TR1 ((20S)-2α,3β, 12β,24(S)-pentahydroxydammar-25-ene 20-O-β-d-glucopyranoside), a dammarane-type gynosaponin, is isolated from the Chinese herbal medicine Jiaogulan (*Gynostemma pentaphyllum*). Gynosaponin TR1 has demonstrated selectivity toward activation of LXRα in HEK293 cells, and enhances LXR-mediated transcriptional activation, expression of ABCA1 and ApoE gene and secretion in THP-1-derived macrophages[17]. Podocarpic acid is a natural non-steroidal LXR agonists derived from plant resins. It has been reported that podocarpic acid is able to bind to LXRα and LXRβ. In hamster and mouse

**Table 2** Exogenous natural agonist of LXRs

| Component | Effects on LXRs | Source | Ref. |
|---|---|---|---|
| Sitosterol and sitostanol | Activation of LXRα/β | Plants | [61,62,63] |
| Diterpenes | Activation of LXRα/β | *Scoparia dulcis.* | [64] |
| Gynosaponin TR1 | Activation of LXRα | *Gynostemma pentaphyllum* | [17] |
| Acanthoic acid | Activation of LXRα | Rollinia | [65] |
| Fucosterol | Agonist of LXRα/β | Marine algae | [66] |
| YT-32 | Agonist of LXRα/β | Tergosterol | [67] |
| Podocarpic acid | Agonist of LXRα/β | Plant resin | [68] |
| Honokiol | Activator of LXR/RXR heterodimer | *Magnolia abovata* | [69,70] |
| Paeoniflorin | Agonist of LXRα/β | *Paeonia lactiflora Pall.* | [71] |
| Iristectorigenin B | Agonist of LXRα/β | *Belamcanda chinensis* | [72] |
| Ethyl 2,4,6-trihydroxybenzoate | Agonist of LXRα/β | *Celtis biondii* | [73] |
| Cyanidin | Agonist of LXRα/β | Fruits and vegetables | [74] |
| Cineole | Agonist of LXRα/β | Teas and herbs | [75] |
| Paxillin | Agonist of LXR | *Penicillium paxilli* fungus | [76] |
| Ergostan-4,6,8,22-tetraen-3-one | Agonist of LXR | *Tolypocladium niveum* fungus | [77] |

LXR: liver X receptor; RXR: retinoid X receptor.

models, it increases plasma HDL-cholesterol by 26%, decreases LDL by 10.6%, and increases triglyceride by 51%[68]. More recently, it has been shown that honokiol, extracted from the bark of Houpu (*Magnolia officinalis*), activates LXR transactivity, in a reporter assay, increases ABCA1 mRNA and protein levels in a dose-dependent manner in U251-MG cells and increases ABCA1, ABCG1 and ApoE expression levels in THP-1 macrophages[69]. Similarly, honokiol increases ABCA1 gene expression in peritoneal macrophages[70]. Paeoniflorin (*Paeonia lactiflora* Pall.), is one of the active ingredients of Shaoyao, an herbal medicine with anti-hyperlipidemic, neuroprotective, and anti-hepatofibrosis effects. Reporter assays show that paeoniflorin transactivates GAL4, rat cholesterol 7α-hydroxylase, phospholipid transfer protein, and ABCA1 gene promoters in a dose-dependent manner, indicating that paeoniflorin might exert pharmacological effects through the LXR pathway[71]. Iristectorigenin B, isolated from Shegan (*Belamcanda chinensis*), stimulates the transcriptional activity of both LXRα and LXRβ. In macrophages, iristectorigenin B suppresses cholesterol accumulation and induces the transcriptional activation of LXRα/β-responsive genes ABCA1 and ABCG1, but not SREBP-1c, FAS, or stearoyl-CoA desaturase-1. It does not induce hepatic lipid accumulation nor the expression of LXR target genes[72]. Ethyl 2,4,6-trihydroxybenzoate (ETB), isolated from *Celtis biondii*, directly binds to and stimulates the transcriptional activity of LXRα and LXRβ. ETB suppresses cellular cholesterol accumulation and induces the transcriptional activation of LXRα/β-responsive genes in macrophages, hepatocytes, and intestinal cells without induction of lipogenic gene expression or cellular triglyceride accumulation in hepatocytes[73].

Cyanidin, a natural flavonoid found in many fruits and vegetable, is known to regulate cellular lipid metabolism. Cyanidin has been reported to induce the transactivation of LXRs and bind directly to the ligand-binding domain of both LXRα and LXRβ, inducing the recruitment of co-activator peptide for LXRα and LXRβ. Following cyanidin stimulation, intracellular cholesterol is reduced and SREBP-1c gene expression is increased in macrophages and hepatocytes, demonstrating that cyanidin is a direct ligand for both LXRα and LXRβ[74].

Cineole is a small aromatic compound purified from teas and herbs. Cineole has been shown to stimulate the transactivation of LXRα and LXRβ, and increase the expression of ABCA1 and ABCG1 in macrophages. Interestingly, in hepatocytes stimulated with cineole, expression of LXRα and LXRα-responsive genes FAS and stearoyl-CoA desaturase-1 was reduced significantly. These results suggest that cineole selectively activates the expression of LXR target genes in reverse cholesterol transport in macrophages without inducing lipogenesis in hepatocytes, which may be used for the development of hypocholesterolemic or anti-atherosclerotic agents[75].

Besides plants, some fungal derivatives also activate LXRs. These include paxillin from *Penicillium paxilli*[76], and ergostan-4,6,8,22-tetraen-3-one, an ergostane derived from *Tolypocladium niveum*, a fungus from Norwegian soil[77].

### 4.4 Antagonist ligands from plants and fungi

The research and development of LXR ligands have been focused on the agonist in the last decade. However, recent studies have shown that a few natural antagonists could lower triglycerides and improve fatty liver without increasing total cholesterol. Thus, the antagonist may also be developed for treatment of diseases. Several natural LXR antagonists and inhibitors have been reported to exert influence on the metabolic disorders (Table 3).

**Table 3** Exogenous natural antagonist and inhibitor of LXRs

| Component | Effects on LXRs | Source | Ref. |
|---|---|---|---|
| Guttiferone I | Antagonist of LXRα | *Garcinia humilis* | [78] |
| Riccardin C | Antagonist of LXRβ | *Blasia pusilla* | [79] |
| Riccardin F | Antagonist of LXRα/β | *Blasia pusilla* | [79] |
| Naringenin | Antagonist of LXRα | Grapefruit, orange, tomato | [80] |
| Genistein | Inhibition of LXRα or activation of LXRβ | Soy | [81] |
| Taurine | Antagonist of LXRα | Seafood | [82] |
| Rhein | Antagonist of LXRα/β | *Rheum palmatum L.* | [83] |
| White button mushroom extract | Inhibition of LXR | *Agaricus bisporus* | [84] |
| Extract of kuding tea | LXRβ antagonism | *Ilex kudingcha C. J. Tseng* | [85] |
| Okra polysaccharide | Inhibition of LXR | Okra pod | [86] |
| Extract of *Parthenocissua tricuspidata* | Inhibition of LXRα | *Parthenocissua tricuspidata* | [87] |
| Extract of *Euscaphis japonica* | Inhibition of LXRα | *Euscaphis japonica* | [87] |

LXR: liver X receptor.

Guttiferone is a new polyisoprenylated benzophenone purified from *Garcinia humilis*, a fruit known as achacha in Bolivia. Guttiferone binds to LXRα selectively[78], however, it is unable to increase the recruitment of co-activators. Riccardin is a natural LXR antagonist compound isolated from liverwort *Blasia pusilla*[79]. Riccardin C is a selective antagonist of LXRβ and can enhance ABCA1 and ABCG1 expression and cellular cholesterol efflux in THP-1 macrophages. Riccardin F is a natural dual antagonist for both LXR isoforms. Both riccardin C and riccardin F compete with the endogenous or synthetic LXR ligand for LXR activation[79]. Goldwasser *et al*[80] have shown that naringenin, a flavanone found in grapefruit, oranges and tomatoes, antagonizes the transactivity of LXRα. Naringenin activates the ligand-binding domain of both peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor-δ while it inhibits the recruitment of LXRα co-activator TRAP-222 in presence of T0901317. It also inhibits the expression of LXRα target genes such as FAS, ABCA1, and ABCG1, and increases fatty acid oxidation in primary rat hepatocytes[80]. Genistein is another flavone LXR modulator isolated from soy. Genistein suppresses the activation of LXRα while it stimulates the activation of LXRβ, resulting in different biological effects for each LXR isoform[81].

Taurine, which is abundant in seafood, is used as an antiatherogenic medicine. Hoang *et al*[82] reported that taurine binds directly to LXRα, and reduces cellular cholesterol in macrophage cells, with the induction of ABCA1 and ABCG1 gene and protein expression. In hepatocytes, taurine significantly induces Insig-2a levels and delays nuclear translocation of the SREBP-1 protein, resulting in a reduction in the cellular lipid levels without inducing the expression of fatty acid synthesis genes[82], suggesting that taurine is a direct LXRα antagonist. Rhein, a lipophilic anthraquinone derived from a traditional Chinese herbal medicine Dahuang (*Rheum palmatum* L.), has been shown to act as an antagonist to LXRα and LXRβ in mice, reducing body weight and serum lipids, and ameliorating nonalcoholic fatty liver disease and associated disorders[83].

Several extracts have been shown to inhibit LXR transactivities, but the active constituents still needed to be identified. White button mushroom, *Agaricus bisporus*, has protective effects against liver steatosis in ovariectomized mice, and down-regulates the expression of genes related to the fatty acid biosynthesis in the liver of mice. *In vitro* mechanistic studies using the HepG2 cell line show that the down-regulation of the expression of FAS and fatly acid elongase 6 by white button mushroom extract is achieved through inhibition of LXR signaling and its downstream transcriptional factor SREBP-1c[84].

Extract of kuding tea, known as *Ilex kudingcha* C. J. Tseng, a traditional beverage in China, inhibits 3T3L1 adipocyte differentiation and hyperlipidemia and fatty liver in high-fat diet-fed mice through selective antagonism of LXRβ transactivity[85]. Okra polysaccharide also has been reported to suppress the expression of LXR pathway genes in high-fat diet-fed mice[86]. Extracts of *Parthenocissua tricuspidata* (Virginia creeper) and *Euscaphis japonica* (Korean sweetheart tree) suppress the transcriptional activity of LXRα as well as the expression of LXRα target genes[87]. Both extracts exert repressive effects on adipocyte differentiation and on lipid metabolism *in vitro*. However, the active compound has not yet been identified from these plants.

Interestingly, the natural modulators of LXR have various structures different from oxysterol, which suggests that the pharmacology of LXR and the discovery of natural ligands are at the beginning of their history. The inhibition of LXR signaling shows significant therapeutic effects on hyperlipidemia and related disorders, suggesting that LXR antagonist may have potential application in the future.

## 5 Conclusions

LXR-deficient mice have shown the association of LXR-signaling pathway dysfunction with several human pathologies including atherosclerosis, hyperlipidemia, AD and cancer. As of the writing of this article, all recent efforts in the targeting LXR for treating these diseases have failed because of adverse side effects. Treatment with synthetic LXR agonists does lower hypercholesterolemia; however, it increases triglyceride and induces fatty liver in animals. Selective liver X modulators (SLiMs)[7,8] or tissue-specific agonists may be developed as a hypercholesterolemia-lowering drug. For example, the development of a liver-specific LXRβ ligand would be beneficial to hypercholesterolemia or atherosclerosis. Also, the screening of agonists from natural sources could be of interest for developing nutraceuticals for the treatment or prevention of these diseases. They make excellent candidates for treatment options, as their activity is mild and their traditional uses in diet and herbal medicine indicate that they are well tolerated. On the other hand, LXR antagonist may be effective to alleviate hypertriglyceridemia, steatosis and probably obesity and insulin resistance. A few studies have shown that inhibition of LXR transactivity could lower triglyceride levels and improve fatty liver without inducing high serum cholesterol levels. In the future, the antagonists of LXR may also be developed as therapeutic drugs that lower triglycerides and improve the condition of fatty liver. Oxysterol-like agonists may specifically activate LXR in the intestine, inhibiting the absorption of cholesterol. The natural source of oxysterol-like molecules may also be useful for such an application. The activity of a ligand could be modulated by specific cofactors that would alter its effects. This would allow the development of selective LXR modulators that

activate LXR in specific tissues to avoid any potential side effect. Natural LXR agonist compounds may be used as nutraceuticals to prevent or treat these disorders.

## 6 Conflict of interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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