Pharmacological Research 219 (2025) 107861

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Liver X receptors: A therapeutic target in demyelinating disorders

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ARTICLE INFO

Keywords:
Liver X receptors
Demyelinating disorders
(Re)myelination
Pharmacological compounds
Plant-based compounds

ABSTRACT

Liver X Receptors (LXRα and LXRβ) are nuclear receptors that regulate various metabolic processes via transcriptional regulation, including lipid and cholesterol homeostasis. Recent evidence highlights the involvement of LXR activation in myelin synthesis and maintenance. Given the essential role of myelin in neuronal communication, its loss in disorders such as multiple sclerosis and Alzheimer's disease underlines the urgent need for effective remyelinating therapies. Restoring the functions of oligodendrocytes to stimulate remyelination offers an interesting approach to protect neurons and slow down neurodegeneration. LXRs have been suggested as potential therapeutic targets in demyelinating disorders as they can promote cholesterol turnover and reduce inflammation, creating a favorable environment for remyelination. Furthermore, activation of LXR directly enhances remyelination by inducing myelin genes. Since various literature and research describe the potential neuroprotective and (re)myelinating benefits of LXR, this review discusses the role of the LXR pathway in (re)myelinating strategies. It highlights the pharmacological compounds for LXR activation, as well as naturally occurring LXR agonists with potential therapeutic value for promoting remyelination.

1. An introduction to liver X receptors

Liver X Receptors (LXRs) are ligand-activated nuclear receptors that modulate various metabolic pathways via transcriptional regulation, including cholesterol and lipid metabolism [1]. There are two LXR isoforms, LXRα (*NR1H3*) and LXRβ (*NR1H2*), with distinct tissue distributions despite having highly similar sequences. LXRα is abundant in metabolically active tissues and cell types such as the liver, intestine, adipose tissue, and macrophages, while LXRβ is expressed more ubiquitously and at higher levels in the central nervous system (CNS) compared to LXRα [2,3]. Both isoforms share a conserved domain organization typical of nuclear receptors: (I) an N-terminal ligand-independent activation function domain (AF-1), which is required for the binding of coregulators, (II) a DNA-binding domain (DBD) consisting of two zinc fingers that recognize LXR response elements (LXREs) in the promoters of target genes, (III) a hydrophobic ligand-binding domain (LBD) necessary for ligand recognition and plays the predominant role in heterodimerization with retinoid X receptors (RXRs), and (IV) an activation function-2 (AF-2) domain within the LBD that binds co-activators to stimulate the transcription of target genes [4]. The DBD and LBD of LXRα and LXRβ have 75.6 % and 74 % sequence homology, respectively [5].

LXRs are activated by endogenous side-chain oxygenated oxysterols, which are cholesterol derivatives, such as 24(S)-hydroxycholesterol (24(S)-OHC), and by intermediates in the cholesterol biosynthetic pathway, such as desmosterol (Fig. 1) [6]. LXRs form obligatory heterodimers with RXRs. In the absence of ligands, nuclear receptor corepressor (N-CoR) and silent mediator of retinoic acid receptor and thyroid receptor (SMRT) are recruited to the LXR-RXR complex to inhibit transcription of LXR target genes by binding to LXREs [7,8]. Upon ligand

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https://doi.org/10.1016/j.phrs.2025.107861
Received 26 May 2025; Received in revised form 8 July 2025; Accepted 15 July 2025
Available online 20 July 2025

binding, a conformational change in the LBD causes the two co-repressors to dissociate from the LXR-RXR complex, facilitating co-activator recruitment. This conformational change enables the complex to bind LXREs, thereby modulating the transcription of target genes involved in biological processes, including lipid metabolism by directly inducing genes central to reverse cholesterol transport (Fig. 1A) [9,10]. In addition to its role in lipid metabolism, LXRs exert anti-inflammatory effects by transrepressing pro-inflammatory genes (Fig. 1B), and LXR activation has been linked to regulating genes involved in myelin synthesis and maintenance (Fig. 1A) [11]. Their dual role in activation and repression allows fine-tuned regulation of metabolic and immune homeostasis [9,10]. As both processes are essential in demyelinating diseases, the link between LXRs and myelin repair is the topic of this review.

2. Connecting LXRs and myelin repair in the CNS

Myelin has a critical role in neuronal communication by acting as an electrical insulator, providing metabolic support, maintaining structural integrity and function of axons, and responding to neuronal activity by remodeling through activity-induced myelination and adaptive myelination. During adaptive myelination, the myelin sheath dynamically adapts to neuronal activity, thereby fine-tuning neural circuits essential for supporting various cognitive activities, including learning and memory [14,15]. Myelin is a specialized extension of glial cell membranes, formed by oligodendrocytes (OLs) in the CNS and by Schwann cells in the peripheral nervous system (PNS), creating multilayered sheaths that wrap around neuronal axons. The unique lipid composition of myelin, particularly its high total lipid content (~40 %), is essential for maintaining membrane rigidity and low permeability. These biophysical properties directly contribute to its insulating function, enabling saltatory conduction. Structurally, myelin is characterized by a high lipid-to-protein ratio (70–85 % lipids vs. 15–30 % proteins) [16]. This composition contrasts with typical cellular membranes with a lipid-to-protein ratio close to 1:1 (i.e., ~50 % lipids by mass). The elevated lipid content supports the formation of tightly packed microdomains rich in cholesterol and sphingolipids that are critical for membrane compaction and hence facilitate nerve saltatory conduction [17,18].

Since myelin is crucial for rapid nerve conduction and axonal support, its disruption in demyelinating disorders leads to impaired neuronal communication and neurodegeneration [19,20]. Demyelination, or the pathological loss of myelin, can occur via two primary mechanisms: primary demyelination results from a direct insult to OLs or Schwann cells (the myelinating cells of CNS and PNS, respectively), while secondary demyelination results from primary axonal loss [21]. During demyelination, cholesterol and other lipids are released from the damaged myelin. Recycling cholesterol by astrocytes, microglia, and macrophages is essential for maintaining cellular lipid homeostasis, a process in which LXRs play a central regulatory role [22,23].

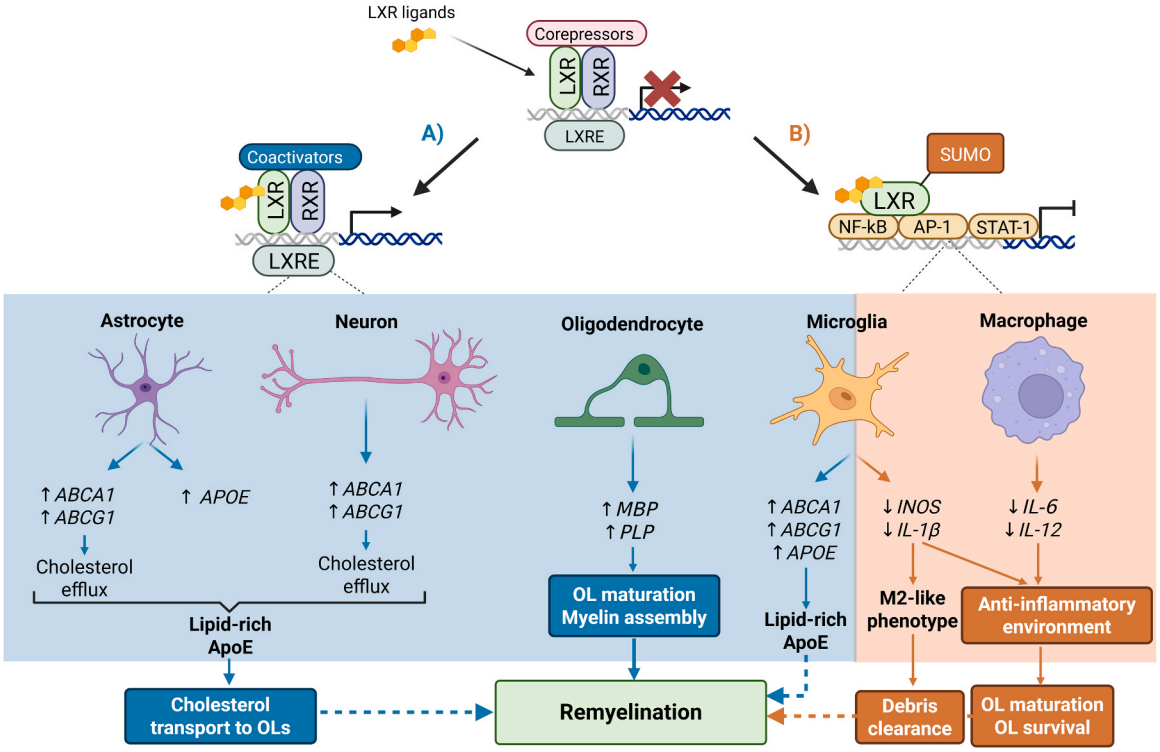


Fig. 1. Activation of LXR promotes remyelination through direct and indirect mechanisms in the CNS. In the presence of LXR ligands (e.g. oxysterols), LXRs undergo a conformational change that dissociates the corepressor complex. **A)** A coactivator complex binds to the LXR-RXR complex and promotes transcriptional regulation of target genes. Direct mechanisms (full arrow) include upregulation of myelin gene expression, MBP and PLP, in OLs, as they promote OL maturation and myelin assembly, which directly leads to remyelination. Indirect mechanisms (dotted arrows) include upregulating genes (ABCA1, ABCG1, APOE) with regulatory functions in the cholesterol turnover in astrocytes, neurons and microglia. Upregulating these genes increases cholesterol efflux and levels of ApoE, resulting in lipid-rich ApoE transporting cholesterol towards OLs. This indirectly leads to remyelination, as the OLs receive the building blocks for myelin assembly. B) SUMOylated LXR represses NF-κB, AP-1, and STAT1, thereby downregulating pro-inflammatory target genes (e.g., IL-1β, IL-6) in microglia and macrophages, causing a anti-inflammatory environment. This environment stimulates OL maturation and OL survival, and is therefore another indirect mechanism for remyelination. Due to the repression of pro-inflammatory factors, microglia will switch towards an anti-inflammatory, M2-like phenotype, which clears debris, this way aiding to an pro-remyelinating environment. Created in BioRender. (2025), https://BioRender.com/6ifpkmw, based on Zhang R. et al. [12] and Courtney R. et al. [13]. ABCA1, ATP binding cassette subfamily A member 1; ABCG 1, ATP binding cassette subfamily G member 1; APOE, apolipoprotein E; AP-1, activator protein 1; CNS, central nervous system; IL, interleukin; INOS, inducible nitric oxide synthase; LXR, liver x receptor; LXRE, LXR response element; MBP, myelin basic protein; NF-κB, nuclear factor kappa B; OL, oligodendrocyte; PLP, proteolipid protein; RXR, retinoid x receptor; STAT1, signal transducer and activator of transcription 1.

Additionally, perturbation of the CNS cholesterol metabolism and impaired LXR signaling are involved in demyelinating diseases, such as multiple sclerosis (MS) and Alzheimer's disease (AD) [24]. Emerging evidence suggests that the dysregulation of lipid metabolism is a hallmark of demyelinating diseases such as MS and Alzheimer's disease (AD), with demyelinated lesions showing reduced cholesterol synthesis, disrupted lipid transport, and accumulation of toxic sterol intermediates [24,25]. LXR/RXR heterodimers, highly expressed in active MS lesions, coordinate both cholesterol metabolism and anti-inflammatory responses in phagocytes, positioning LXR as a key regulator in disease progression [24]. By upregulating ABCA1/ABCG1 and driving ApoE lipidation, LXR agonists help generate lipid-rich particles that are taken up by OLs via low-density lipoprotein receptor (LDLR) and low-density lipoprotein receptor-related protein-1 (LRP1), directly providing the essential lipids required for remyelination [23,24,26,27].

In the context of demyelination, excessive release of cholesterol and myelin debris results from the breakdown of oligodendrocyte membranes. Efficient clearance and recycling of this lipid-rich debris are essential for remyelination. However, when LXR signaling is impaired, cholesterol efflux pathways are downregulated, leading to intracellular lipid accumulation in glial cells. In microglia and phagocytes, the buildup of cholesterol esters and lipid droplets contributes to a foamy, dysfunctional phenotype associated with impaired debris clearance and chronic inflammation [28–30]. Macrophages similarly fail to adequately process myelin debris, further aggravating the pro-inflammatory environment. Moreover, astrocytic LXR dysfunction disrupts lipid transport and reduces metabolic support to oligodendrocyte lineage cells, compounding the deficit in myelin membrane synthesis [23,24]. This environment inhibits OPC differentiation and maturation into myelinating oligodendrocytes, thereby stalling remyelination. Thus, LXR plays a central role at the intersection of lipid metabolism and neuroinflammation in demyelinating conditions [31].

Following demyelination, a regenerative process called remyelination will be initiated, which repairs and restores the damaged myelin sheath. Accumulation of myelin debris, in particular, is a significant inhibitor of remyelination, so proper debris clearance creates a permissive environment for remyelination. Both CNS and PNS remyelination gained a lot of scientific interest, with distinct differences between the two systems. In particular, Schwann cells facilitate more efficient remyelination in the PNS, aided by rapid clearance of myelin debris and a supportive extracellular environment [32]. Remyelination in the CNS is mediated either by existing OLs that contribute to remyelination or by OPCs that proliferate, migrate to the site of damage, and differentiate into mature, myelinating OLs. OPC differentiation is guided by signals from multiple cell types [33]. This process begins with neuronal activity, which triggers changes in OPCs that prime them to mature [34]. Supportive immune cells, such as M2-like polarized microglia, promote repair by clearing debris and secreting factors that promote differentiation and myelination [16,35,36]. Astrocytes attract OPCs to the lesion site, support their development, and help provide necessary lipids [37]. Furthermore, regulatory T-cells also enhance this process by releasing growth factors and reducing harmful inflammation [38,39]. Furthermore, endothelial cells contribute by releasing supportive signals and encouraging a healing immune environment [40]. In addition, OLs that survive demyelination can also induce remyelination [41]. However, these surviving OLs typically form only two new sheaths per cell (compared to 15 prior to demyelination), and often mistarget newly made myelin to neuronal cell bodies rather than axons [41]. Even though the original thickness of the myelin sheath will not be achieved, remyelination generally leads to functional recovery, improved nerve conduction velocity, and metabolic support to the axon [18,21,42].

In demyelinating diseases, CNS remyelination is hindered by inhibitory factors such as persistent myelin debris, an inflammatory environment, a less permissive extracellular matrix, and the formation of glial scars [31]. The extent of recovery is highly variable, influenced by age, disease context, and the lesion environment. Aging, for example, reduces OPC recruitment and differentiation capacity, and chronic inflammation in certain diseases can further hinder repair [43]. Emerging evidence highlights the neuroprotective and remyelinating potential of LXR activation, particularly through its regulation of cholesterol metabolism and inflammation, making its role in CNS (re) myelination a critical target for therapeutic interventions [23]. However, LXR activation can have contrasting effects in the CNS and PNS. Recent findings demonstrated that LXR activation in the PNS downregulates key myelin genes, such as myelin protein zero (MPZ) and peripheral myelin protein-22 (PMP-22), via cross-talk with the Wnt/β-catenin pathway in a mouse Schwann cell line (MSC80) [44,45,11]. This inhibitory effect suggests that LXR activation could hinder remyelination in the PNS, providing further rationale to limit the scope to the CNS [44,45,11]. Given these contrasting effects, it is crucial to delineate how LXR activation impacts myelin repair mechanisms in the CNS. Therefore, this review elaborates on how LXR activation influences CNS (re)myelination by modulating cholesterol metabolism, inflammatory responses, and the function of key glial and immune cell populations involved in myelin repair.

3. The functions of LXRs in remyelination

Remyelination is critically dependent on an adequate and timely supply of cholesterol, a major lipid constituent of the myelin sheath. While OLs can synthesize cholesterol de novo, this capacity becomes insufficient under pathological conditions such as MS, where extensive lipid turnover and inflammatory stress impair biosynthesis pathways [24]. LXR activation supports remyelination through direct and indirect mechanisms (Fig. 1). Activation of LXRs promotes OL differentiation and has been associated with increased expression of proteolipid protein (*PLP)* and myelin basic protein (*MBP)*, necessary in OL maturation and myelin assembly [11]. In a study by *Meffre et al.*, deletion of LXR in OPCs was shown to impair myelination. At the same time, treatment with a synthetic LXR agonist enhanced the expression of myelin genes, promoted OL maturation, and supported remyelination in demyelinated brain slices [11]. Besides the direct effect, activation of LXRs in astrocytes, microglia, and to some extent in OLs, can (in)directly support the remyelination process by promoting cholesterol turnover and reducing inflammation [46]. Cholesterol turnover is promoted by upregulating reverse cholesterol transport (RCT) genes, such as ATP-binding cassette subfamily A member 1 *(ABCA1)* and ATP-binding cassette subfamily G member 1 *(ABCG1)*, which facilitate the efflux of cholesterol and other lipids to extracellular acceptors such as apolipoprotein E (ApoE) (Fig. 1A). This process results in the generation of lipid-rich ApoE particles, which prevent cytotoxic lipid accumulation and ensure an adequate supply of cholesterol towards OLs for myelin synthesis [13]. Cholesterol turnover is considered more important in astrocytes, as they provide cholesterol to OLs for incorporation into the myelin membranes. This astrocytic supply is critical during development and repair but might be impaired under pathological conditions, where OLs or microglia may play compensatory roles. Recent findings showed that APOE4/4 OLs, carrying the APOE ε4 allele – a genetic variant of the ApoE gene known as a genetic risk factor for late-onset AD –, exhibit intracellular cholesterol accumulation due to disrupted cholesterol trafficking [47]. These alterations in cholesterol in OLs were found to coincide with reduced myelination in APOE4 carriers. The cause of reduced myelination remains under investigation. Facilitating cholesterol transport is therefore hypothesized to support myelination by improving lipid availability and preventing toxic accumulation [47]. Additionally, modulation of ApoE receptors could promote OPC differentiation and remyelination, though the effects may vary depending on the ApoE isoform [48,49]. Activation of RXRs, the obligatory partner of LXRs, can also aid the remyelination process, as administration of bexarotene, a synthetic RXR agonist, resulted in radiological evidence of remyelinating effects in patients with MS in a completed phase IIa clinical trial (isrctn.com; ISRCTN14265371) [50]. However, clinical

benefits were modest or absent, and side effects (e.g., hyperlipidemia) were significant [50]. Activation of LXRs indirectly influences the transcription of lipogenic genes depending on the ligand. Endogenous ligands such as 24(S)-OHC suppress the processing of sterol regulatory element-binding proteins (SREBPs), specifically SREBP-2. This suppression occurs via the stabilization of insulin-induced gene (INSIG) proteins, which inhibit the activation of SREBP-2 [51]. Oxysterols such as 24(S)-OHC bind to INSIG proteins to enhance their interaction with SREBP cleavage-activating proteins (SCAPs), whereas cholesterol and its precursor desmosterol bind directly to SCAP, thereby triggering INSIG proteins to bind to SCAP [52]. These interactions prevent the SCAP/SREBP complex from translocating to the Golgi, where the complex would otherwise undergo proteolytic cleavage to enter the nucleus. As a result, the activity of SREBPs is suppressed, leading to downregulation of lipid synthesis target genes. This regulatory mechanism is essential for maintaining cholesterol homeostasis, as SREBP-2 is involved in cholesterol biosynthesis and uptake. Moreover, 24(S)-OHC, in contrast with synthetic LXR agonists, does not upregulate the expression of *SREBP-1c* [53]. Following the suppression of *SREBP-2* and *SREBP-1c*, glucose and fatty acid biosynthesis genes are downregulated, leading to decreased serum cholesterol and triglyceride levels [54,55].

Beyond facilitating cholesterol transport, activation of LXRs inhibits inflammation via transrepression of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway (Fig. 1B) [56]. By attaching small ubiquitin-like modifier (SUMO) proteins, SUMOylated LXR represses NF-κB, AP-1, and signal transducer and activator of transcription 1 (STAT-1), resulting in the downregulation of pro-inflammatory target genes, such as *IL-1β* and *IL-12*. A pro-inflammatory environment strongly inhibits the differentiation, maturation, and survival of OLs, thereby reducing remyelination [31]. Activation of LXRs shifts microglia away from a pro-inflammatory phenotype towards the M2-like phenotype, thereby supporting remyelination by providing debris clearance [29]. Thus, activation of LXRs influences lipid metabolism and inflammation, making LXRs promising therapeutic targets for neurodegenerative diseases in which remyelination is essential.

4. Pharmacological LXR agonists

Activating LXRs can enhance remyelination directly by promoting myelin gene expression or indirectly by stimulating cholesterol turnover in astrocytes, microglia, and OLs, and by decreasing inflammation [11,57–59]. Therefore, pharmacological LXR agonists hold therapeutic potential for demyelinating disorders. The effectiveness of LXR activation may depend on the specific LXR subtype expressed in glial cells. In mice, OPCs and OLs express higher levels of LXRβ compared to LXRα [60,61]. In humans, however, the data regarding LXRα and LXRβ expression levels are less consistent [62]. Despite the variability, LXRβ is considered to have a wider tissue distribution, including expression in glial cells and the CNS [61,62].

The first-generation synthetic agonists, such as T09 and GW3965, were designed to activate both LXRα and LXRβ. T09 induces the expression of LXR target genes such as *ABCA1*. Moreover, T09 promotes myelin gene expression and OL maturation in primary glial cells [11]. This pro-remyelinating effect was further confirmed in cerebellar lysolecithin-induced demyelinated organotypic cultures, where T09 significantly enhanced remyelination. Importantly, T09 failed to rescue demyelination in LXRα/β double knockout (KO) cultures, indicating that remyelination depends on the presence of LXR [11]. Besides the beneficial effects of remyelination, T09 exhibits potent anti-inflammatory properties in the CNS, as evidenced by its protective role in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS [63,64]. Similar anti-inflammatory and remyelination-promoting effects have also been observed with the pan-LXR agonist GW3965 [30,64]. In aged mice with lysolecithin-induced demyelinated lesions, defective cholesterol clearance by phagocytes has been observed [30]. This impaired cholesterol efflux leads to lysosomal rupture and inflammasome activation, exacerbating inflammation and thereby impeding remyelination. Oral administration of GW3965 in these aged mice enhanced remyelination by reducing neuroinflammation and promoting RCT [30]. Unfortunately, both T09 and GW3965 induce lipogenesis, resulting in adverse effects such as hepatic steatosis and hypertriglyceridemia. Increased lipogenesis is a consequence of activating the SREBP-1c pathway in the liver, mediated by LXRα-induced transcription of lipogenic genes *Srebp-1c, Fas,* and *Acc1*, as found in a study using C57BL/6 J mice [2,65]. Therefore, the search for novel LXR agonists is focused on compounds that activate LXR without inducing the SREBP-1c pathway. To achieve this, four strategies are being followed: LXRβ-specific activation, tissue-specific activation, mimetics of endogenous ligands, or enzymes that increase the concentration of endogenous ligands.

The approach to identify or develop LXRβ-selective agonists is challenging since the ligand binding domains of LXRα and LXRβ are highly similar, making it difficult to find or establish agonists that distinguish between LXRα and LXRβ [66,67]. Still, a few preferentially activating LXRβ agonists have been described, for instance, LXR-623, CS-8080, and BMS-779788. LXR-623 showed promising anti-atherogenic results and did not activate lipogenesis in the liver of a murine LDLR (-/-) atherosclerosis model [68]. In addition, in a phase I clinical trial (ClinicalTrials.gov ID: NCT00366522), LXR-623 activated *ABCA1* and *ABCG1* expression in blood samples of healthy individuals [69]. However, LXR-623 also induced CNS-related adverse effects, including lightheadedness, confusion, palpitations, and paranoid ideation [69]. The other two compounds, CS-8080 (ClinicalTrials.gov ID; NCT00613431) and BMS-779788 (ClinicalTrials.gov ID; NCT00836602), did not continue beyond the phase I clinical trial due to unspecified safety concerns [70]. Nevertheless, searching for LXRβ-selective agonists with fewer side effects continues [71–73].

The second category to activate LXR while avoiding the lipogenesis-related adverse effects is to develop tissue-selective LXR agonists. The rationale behind this approach is to activate LXRs selectively in specific tissues, such as the intestine, thereby avoiding lipogenesis in the liver. Tissue-specific LXR agonists such as YT-32, GW6340, and WYE-672 promote intestinal RCT and protect against atherosclerosis in preclinical models without causing liver-related adverse effects [74–77]. However, most of these studies are conducted regarding cardiovascular or metabolic diseases. Their application potential to neurodegeneration is more speculative and indirect; for example, an intestinal-selective agonist might also indirectly affect other organs, potentially via the brain through the gut-brain axis [78]. Nonetheless, tissue-selective LXR agonists still face significant challenges in demonstrating their therapeutic relevance. In particular, designing selective LXR agonists for the CNS remains challenging, as the drug delivery across the blood-brain barrier (BBB) is a well-known issue. Potential solutions are the intranasal or intrathecal drug delivery systems, which may provide a more CNS-specific method of administration [79,80].

A third strategy involves developing synthetic analogs of endogenous LXR agonists, such as desmosterol, which suppress *SREBP-1c* activation and thus minimize the lipogenic adverse effects [81]. Representative examples include N,N-dimethyl-3*β*-hydroxycholenamide (DMHCA) and methylpiperidinyl-3*β*-hydroxycholenamide (MePipHCA), both of which mimic desmosterol's activity while exhibiting improved potency, particularly MePipHCA [82,83]. Both compounds activate LXRs without activating the SREBP pathway, and no lipogenic adverse effects were observed *in vitro* and *in vivo* [82,83]. DMHCA and MePipHCA are still preclinical; confirmation in higher-order preclinical models or human trials is still missing. Notably, the efficacy of endogenous LXR activators—including oxysterols (e.g., 24(S)-OHC, 27-OHC) and cholesterol biosynthesis intermediates (e.g., desmosterol, 24(S),25-epoxycholesterol)—is governed by two critical structural determinants: (I) their side chain oxidized moieties (hydroxyl/epoxy groups) and/or (II) unsaturated side chains [81,82]. These features are conspicuously

absent in poorly active phytosterols (e.g., sitosterol, campesterol), explaining their poor LXR agonism [84]. Aligning with this rationale, three novel side-chain oxysterols LXR agonists— methyl 3β-hydroxychol-5-en-24-oate, methyl (3β)-3-aldehydeoxychol-5-en-24-oate, and 24-ketocholesterol (which has also been identified in brown seaweed)—were recently identified through luciferase reporter assays, demonstrating robust dual activation of LXRα/β [85,86]. These compounds effectively induce the expression of LXR target genes involved in cholesterol homeostasis (*APOE*, *ABCA1*, and *ABCG1*) without significantly affecting lipogenic genes (*SREBP1c*, *FASN*, *SCD1*, and *ACC1*), highlighting their therapeutic potential for modulating cellular cholesterol transport [82,86]. C24-hydroxylated stigmastane derivatives upregulate beneficial LXR targets (e.g., ABCA1), but simultaneously induce lipogenic genes (*SREBP1c, FASN, SCD1*), which may compromise therapeutic utility through metabolic side effects [87].

The fourth option is to target enzymes to increase the concentration of endogenous LXR agonists without activating the SREBP-1c pathway. For instance, CYP46A1 catalyzes the conversion of cholesterol to 24(S)-OHC, and therefore, increasing CYP46A1 activity upregulates the concentration of the endogenous LXR agonist 24(S)-OHC [88]. Increased CYP46A1 activity has already shown beneficial effects in models of AD, Huntington's disease, and other neurodegenerative diseases [88,89]. A phase I clinical trial testing the CYP46A1-activating drug Efavirenz in AD patients has been started, but results are still pending [90]. Using both exogenous (e.g., Efavirenz) and endogenous (neurotransmitter-mimetic) compounds to activate CYP46A1 could offer synergistic benefits, as recent studies demonstrate their distinct allosteric binding sites and complementary kinetic effects [91]. This dual approach may allow lower effective drug doses while maintaining physiological regulatory patterns through neurotransmitter-mediated activation pathways [91]. Another target is *DHCR24*, the enzyme responsible for converting desmosterol to cholesterol. DHCR24 inhibition, for example, by SH42, leads to the accumulation of desmosterol, which acts as an endogenous LXR agonist. SH42 has been shown to selectively enhance LXR activation in macrophages while avoiding the activation of the lipogenic SREBP-1c pathway in hepatocytes, thereby providing a means of cell-specific regulation of LXR activity [82]. Recent studies have expanded on this option by identifying additional DHCR24 inhibitors through virtual screening approaches. Notably, irbesartan, a widely used antihypertensive agent, was found to inhibit DHCR24 activity and exhibit cholesterol-lowering effects *in vitro* and *in vivo* [92]. Although not yet validated in humans, these findings suggest that DHCR24 is a viable and druggable target to influence LXR signaling pathways via desmosterol accumulation.

In conclusion, ongoing research for pharmacological components that activate LXRs has not yet resulted in a compound that can be used clinically.

5. Natural plant-based LXR-activating compounds

Nowadays, there is a growing interest in natural compounds that can activate LXRs due to their potential therapeutic utility while minimizing side effects, such as hypertriglyceridemia and hepatic steatosis [93]. Natural LXR agonists can be classified into six main categories: (oxy) phytosterols, terpenes, flavonoids, alkaloids, phenol derivatives, and others (Table 1). As over 100 possible natural LXR compounds exist, this review lists the most extensively studied plant-based LXR-activating compounds in each category.

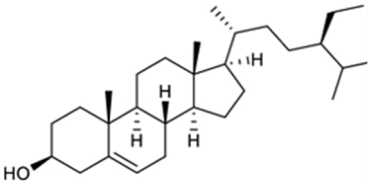
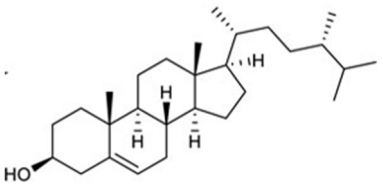
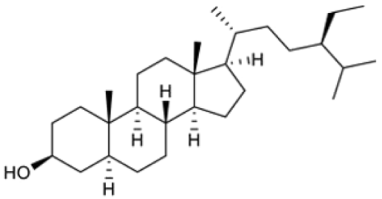
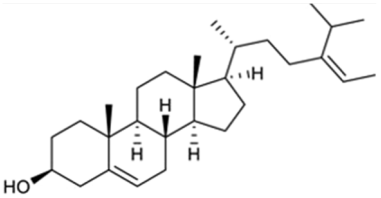
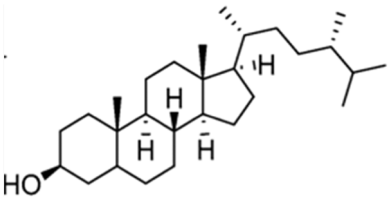
No.; number, Refs; references, 5xFAD; five familial AD mutations, ABCA1; ATP-binding cassette subfamily A member 1, ABCG1; ATP-binding cassette subfamily G member 1, AD; Alzheimer's disease, AGE; advanced glycation end products, Akt; protein kinase B, ALS; amyotrophic lateral sclerosis, APOE; apolipoprotein E, APP; amyloid precursor protein, BACE-1; beta-site amyloid precursor protein cleaving enzyme-1, BCAS; bilateral carotid artery stenosis, Bcl2; B-cell lymphoma 2, BDNF; brain-derived neurotrophic factor, BV2; immortalized microglial cell line, CAT; catalase, CCF-STTG1; human astrocytoma cell line, CCL2; CC chemokine ligand 2; CD68; cluster of differentiation 68, CNS; central nervous system, COX-2; cyclooxygenase-2, CPZ; cuprizone, CRS; chronic restraint stress, CSF; central spinal fluid, CYP46A1; cytochrome P450 family 46 subfamily A member 1, DC; dendritic cell, DHCR24; 24-dehydrocholesterol reductase, EAE; experimental autoimmune encephalomyelitis, ER; endoplasmatic reticulum, FBS; fasting blood sugar, FOXO3a; forkhead box O3, GFAP; glial fibrillary acidic protein, GPx; glutathione peroxidase, GRx; glutathione reductase, GSH; glutathione, GSK-3β; glycogen synthase kinase-3β, HDAC; histone deacetylase, HDL; high-density lipoprotein, HO-1; heme oxygenase-1; Iba1;allograft inflammatory factor 1, IFN-γ; interferon gamma, IL; interleukin, JAK; janus kinase, LTP; long term potentiation, MAG; myelin-associated glycoprotein, MBP; myelin basic protein, MDA; malondialdehyde, MMP-9; matrix metalloprotease 9, MPP+ ; 1-methyl-4-phenylpyridinium, MS; multiple sclerosis, MTPT; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, mTOR; mammalian target of rapamycin, NF-kB; nuclear factor kappa-light-chain-enhancer of activated B cells, NLRP3; nucleotide-binding domain-like receptor family pyrin domain containing 3, NOS-2; nitric oxide synthase 2, Npc1; niemann pick disease type 1, NRf2; nuclear factor erythroid 2-related factor 2, O4; oligodendrocyte marker, OPC; oligodendrocyte precursor cell, PBMC; peripheral blood mononuclear cell, PC; pheochromocytoma cells, PD; Parkinson's disease, PGC-1α; peroxisome proliferator-activated receptor-alpha coactivator, PLP1; proteolipid protein 1, PS1; presenilin 1, ROS; reactive oxygen species, SCI; spinal cord injury, SIRT1; silent information regulatory of transcription 1, SOD; superoxide dismutase, SREBP-1c; sterol regulatory element binding protein 1c, STAT; signal transducer and activator of transcription, Tg; transgenic, Th1; type 1 T helper, TG; triglycerides, TMT; trimethyltin, TNF-α; tumor necrosis factor α, TREM2; triggering receptor expressed on myeloid cells 2, UQCRC1; ubiquinol-cytochrome c reductase core protein 1, Wnt3; wingless-related integration site family member 3

5.1. Phytosterols

Phytosterols are the plant counterpart of mammalian cholesterol. Some phytosterols have been detected in the CNS, suggesting that they may cross the BBB under certain conditions, such as their structure [201]. Despite their structural similarity to cholesterol, phytosterols differ in saturation level and side chain configuration. Several phytosterols and related compounds have been identified with potential LXR-activating properties. However, most phytosterols exhibit only weak or partial agonist activity and are less potent than oxysterols or synthetic ligands. The most frequently encountered phytosterols are β-sitosterol, campesterol, fucosterol, and stigmasterol (Table 1, Nos. 1, 2, 4, and 6, respectively). These natural ligands have recently been of interest as compounds for LXR activation because of their cholesterol-lowering and anti-inflammatory effects [93,108,202]. However, the concentrations required to achieve these biological effects are substantially higher than physiological levels, and their LXR activating potential remains weak [96,203]. Conventional phytosterols, such as β-sitosterol and campesterol, may lower serum cholesterol primarily through competitive absorption inhibition. However, their potential to act as LXR agonists appears limited due to the absence of oxygenated functionalities in their side chain [204,205].

Fucosterol, a predominant phytosterol in brown seaweeds, has been shown to exhibit dual hypocholesterolemic and neuroprotective effects. In human embryonic kidney cells (HEK 293), fucosterol has been reported to activate both LXRα and LXRβ. A human hepatic cell line (HepG2) transcriptionally upregulates cholesterol efflux genes such as *ABCA1* and *ABCG1* [93]. Nevertheless, its agonistic potency is low compared to synthetic or oxysterol-based ligands [95]. Additionally, fucosterol modulates cell surface receptors such as toll-like receptors (TLRs) and major signaling systems such as p38 or extracellular-signal-regulated kinase (ERK) pathway to inhibit

Table 1
The main plant-based LXR-activating compounds according to their category: (oxy)phytosterols, terpenes, flavonoids, alkaloids, phenol derivatives, and others. The compounds are numbered, their structure, research in various demyelinating diseases, and sources are presented. The figures of structures were utilized by *She et al#* and *Zhan et al#* [86,94]. Regarding several (oxy)phytosterols, conflicting data exists (*), as Bogie *et al#* and others could not demonstrate the full LXR activity of these compounds [84,95,96].

Category	No.	Name	Structure	Source	Research	Refs.
(Oxy) phytosterols	1	β-sitosterol*		Cereals, fruits, vegetables, nuts, oils	AD: • SH-SY5Y cells + APP695 (effect:↑ Aβ secretion by ↑ gene expression of β-secretase + ↑ enzyme activity) [97] • Blood platelets (effect: ↓ high cholesterol-induced platelet Aβ-release + no ↑ of β- and γ-secretase activities) [98] • APP/PS1 mouse (effect: ↑ spatial learning, ↑ recognition memory ability, ↓ plaque load) [99] MS: • PBMC *in vitro* (effect: ↓ pro-inflammatory factors (IL−12, TNF-α), ↑ anti-inflammatory factors (IL−10)) [100] • TMT-mice for neurodegeneration (effect: reversed TMT-induced spatial memory deficits, ↓ neuronal death, ↓ oxidative stress, ↑ astrocyte activation) [101]	[84, 102, 103]
	2	Campesterol*		Cereals, fruits, vegetables, berries, oils	AD: • SH-SY5Y cells + APP695 (effect: ↑ γ-secretase activity) [104] • Clinical trial (effect: level campesterol in brain AD patients = healthy control, ↓ 27-OHC due to oxidative damage) [104] MS: • EAE mice model (effect: plant sterol uptake (incl. 25 % campesterol): ↑ anti-inflammatory IL−10, ↓ expression pro-inflammatory factors (CCL2, TNFα, IL−6, IFN-γ)) [105]	[84, 103, 106]
	3	Sitostanol		Coconut oil, tall oil extracts, and some vegetable oils	Hyperlipidemia: • ApoE3-Leiden mice (effect: ↓ serum cholesterol and hepatic cholesterol, no CNS/ myelin endpoints) [107]	[108]
	4	Fucosterol*		Seaweed and macroalgae	AD: • Primary hippocampal neurons exposed to Aβ1–42 (effect: ↓ER stress (↓GRP78), ↑ TrkB-ERK1/2 activation) [109,110] • Rat Aβ1–42-infusion model (effect: ↑ memory performance, ↓ ER stress (↓GRP78), ↑ BDNF) [111] • *In vitro* enzymatic assay (effect: ↓ BACE1, ↓ AChE and BChE)[111] Inflammatory diseases (e.g., MS): • RAW264.7 macrophages (effect: ↓ LPS-induced TNF-α/IL−6)[111] • Rat model (effect: ↑ antioxidant defenses (e.g., GPX1, SOD, CAT, HO−1)[111]	[84, 103]
	5	Campestanol		Coconut oil, tall oil extracts, and some vegetable oils	Niemann-Pick type C1: • Npc1-/- mice (did not assess CNS demyelination or neuroinflammation) [112] Hyperlipidemia: • ApoE3-Leiden mice (effect: ↓ serum cholesterol and hepatic cholesterol, no CNS/ myelin endpoints) [107]	[108]

(*continued on next page*)

Table 1 (*continued*)

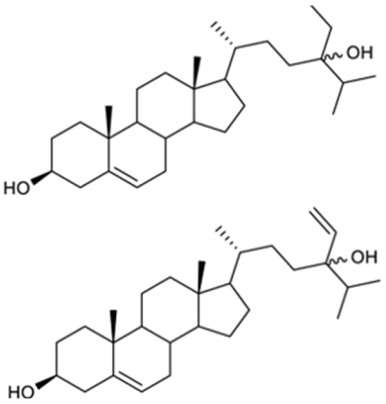
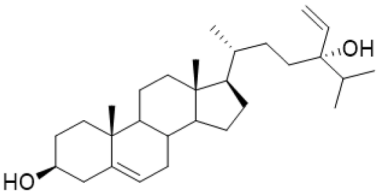
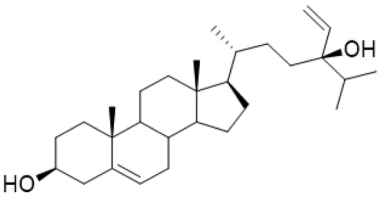
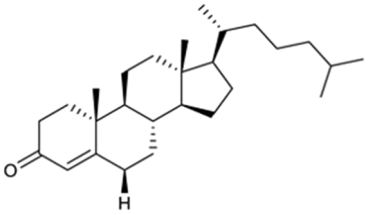
Category	No.	Name	Structure	Source	Research	Refs.
	6	Stigmasterols*		*Ficus pumila* L., brown seaweed (*Sargassum*)	AD: • BV2 microglia + Aβ1–42 (effect: ↓NF-κB and NLRP3, ↓ M1-like phenotype) [113] • SH-SY5Y + APP695 (effect: ↓ Aβ40 and Aβ42)[97] • Male APPswePS1ΔE9 transgenic mice (effect: ↓ brain β- and γ-secretase activity, ↓ brain levels of Aβ40 and Aβ42, after cohort ↓ Aβ plaque burden in cortex and hippocampus and ↓Aβ40) [97] Neurodegeneration: • H_2O_2-treated SH-SY5Y cells (effect: ↓ROS, ↑SIRT1, FOXO3a, Bcl2) [114]	[84,94, 103]
	7	24(S)-Saringosterol		Brown seaweeds	AD: • N2a neuroblastoma cells (effect: ↓ Aβ-plaques) [84] • APPswePS1ΔE9 mice (effect: ↑ cognition, ↓ SREBP-1C, ↑ Iba1)[115,116] AD, MS: • OPCs *in vitro* (effect: ↑O4 expression) [117]	[86, 116, 118]
	8	24(R)-Saringosterol		Brown seaweeds	No direct studies in CNS models	[86, 116, 118]
	9	4-Cholesten−3-one		Plant roots, red marine algae, *Laurencia papillosa*	No direct studies in CNS models	[94]

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Table 1 (*continued*)

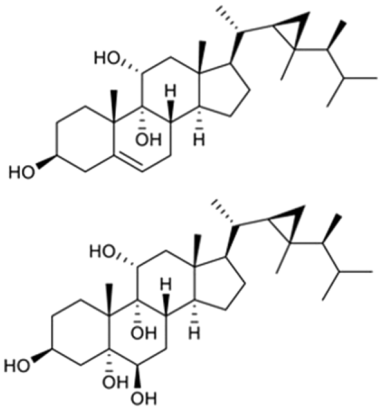
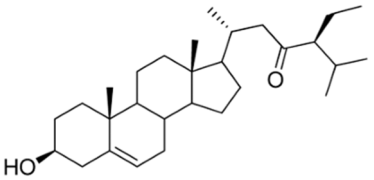
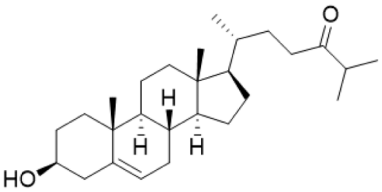
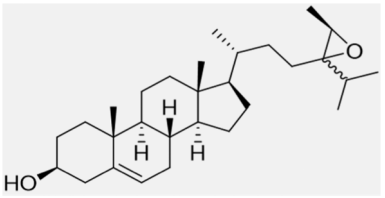
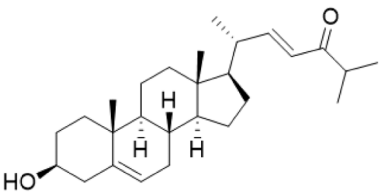
Category	No.	Name	Structure	Source	Research	Refs.
	10	Gorgostane steroids		Corals	No direct studies in CNS models	[119]
	11	22-ketositosterol		*Costus speciosus*, marine sponges	AD: • Human astrocytes and CCF-STTG1 cells (effect: ↑ ABCA1, ABC1, APOE) [120] • APPswePS1ΔE9 mice (effect: ↑ spatial memory, ↓ Iba1, CD68, GFAP) [120]	[120, 121]
	12	24-ketocholesterol		*Sargassum fusiforme*	Neurodegenerative diseases: • CCF-STTG1 cells (effect: ↑ *APOE*, ↑ *ABCA1*, ↑ *ABCG1)* [86] • SH-SY5Y cells (effect: ↑ *CYP46A1*, ↑ *ABCA1*, ↑ *ABCG1*) [86]	[85,86, 116]
	13	fucosterol−24,28 epoxide		*Sargassum fusiforme*	Neurodegenerative diseases: • CCF-STTG1 cells (effect: ↑ *APOE*, ↑ *ABCA1*, ↑ *ABCG1*, ↓ *DHCR24*) [86] • SH-SY5Y cells (effect: ↑ *CYP46A1*, ↑ *ABCA1*, ↑ *ABCG1*) [86]	[122]
	14	(3β,22*E*)−3-hydroxycholesta−5,22-dien−24-one		*Sargassum fusiforme*	Neurodegenerative diseases: • CCF-STTG1 cells (effect: ↑ *APOE*, ↑ *ABCA1*, ↑ *ABCG1*) [86] • SH-SY5Y cells (effect: ↑ *CYP46A1*, ↑ *ABCA1*, ↑ *ABCG1*) [86]	[86]

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Table 1 (*continued*)

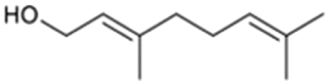
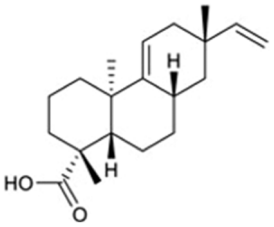
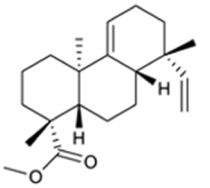
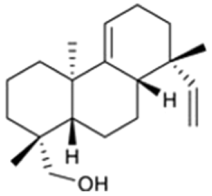
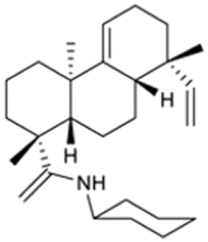
Category	No.	Name	Structure	Source	Research	Refs.
Terpenes	15	Geraniol		Essential oils from aromatic plants	AD: • Rat model induced by intracerebroventricular microinjection of $A\beta_{1-40}$ (effect: improved memory, ↓ Aβ plaque accumulation, ameliorated hippocampal LTP impairment) [123] SCI: • SCI rats (effect: ↓ TNF-α, ↓ IL−1β, ↓ IL−6, ↑ SOD, ↑ GSH, ↓ MDA, ↓ NF-κB) [124]	[125, 126]
	16	Cineole		Eucalyptus oils, teas, rosemary, *Psidium*, and other essential oils	AD: • Aβ toxicated PC12 cells (effect: improved cell viability, ↓ proinflammatory cytokines (TNF-α, IL−1β, IL−6), ↓ NOS−2, ↓ COX−2, and ↓ NF-κB) [127] • AGEs-induced neuronal injury and intracerebroventricular-AGE rats (effect: ameliorate tau phosphorylation by down-regulating activity of GSK−3β, and reduced Aβ production by inhibiting BACE−1 activity) [128]	[93, 129]
	17	Acanthoic acid		Isolated from *Rollinia pittieri* Saff. and *R. exsucca*, *Acanthopanax koreanum Nakai*	No direct studies in CNS models	[93, 130]
	18	Diterpenes (DTP 1, DTP 3, DTP 5)	  	Widespread in plants (e.g., *Scoparia dulcis* L.)	No direct studies in CNS models	[93]

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Table 1 (*continued*)

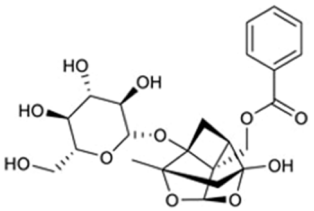
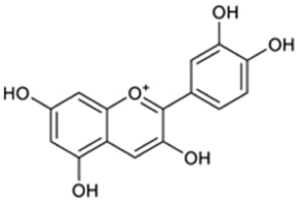
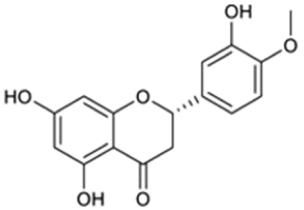
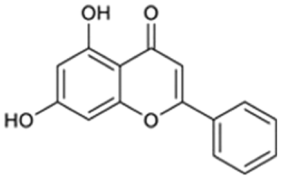
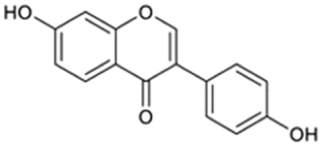
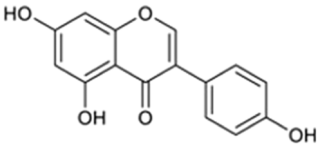
Category	No.	Name	Structure	Source	Research	Refs.
	19	Paeoniflorin		*Paeonia lactiflora*	AD • 5xFAD mice (effect: improved memory, alleviated Aβ burden, inhibited astrocyte activation, ↓ IL−1β, ↓ TNF-α via adenosine A1 receptor) [131] MS: • EAE mouse model (effect: ameliorated clinical symptoms and onset of EAE, decreased CNS infiltration of Th17 cells by suppressing the expression of costimulatory molecules and the production of IL−6 of DCs) [132]	[94, 133]
Flavonoids	20	Cyanidin		Fruits and vegetables	AD: • Bisphenol A-induced rat model (effect: improved memory, ↓ phosphorylated tau, ↓ GSK3β, restored Wnt3 and β-catenin levels) [134]	[135, 136]
	21	Hesperetin		Orange peels and other citrus fruits	AD: • Rats induced with streptozotocin (effect: improved memory and ↑ activity of antioxidant enzymes (SOD, GPx, GRx and CAT) [137] MS: • Lysolecithin-induced focal demyelination model (effect: ↓ number of astrocytes and microglia, ↓ extent of demyelination area) [138]	[94, 139]
	22	Chrysin		Honey, propolis, plant extracts	AD: • Aged female mice induced by $A\beta_{1-42}$ (effect: improved memory via attenuation of oxidative stress and neuroinflammation) [140] MS: • EAE mouse model (effect: reduced weight loss, block HDAC and GSK−3β expression and reduce neuroinflammation) [141]	[142]
	23	Daidzein		Soybeans	Cerebral ischemia/reperfusion injury: • ICR rats (effect: improved neurological deficits, infarct volume, and brain edema via Akt/mTOR/BDNF signaling pathway) [143] PD: • MPTP-induced mouse model (effect: improved motor function, reduced dopaminergic neuron loss, and restored dopamine levels via Nrf2 pathway) [144]	[145, 146]
	24	Genistein		Soybeans	AD: • APP/PS1 AD mouse model (effect: ↓ Aβ aggregation and microglial reactivity, improved cognitive performance) [147] • Clinical trial NCT01982578 (effect: improvement in Complutense Verbal Learning Test and Rey Complex Figure Test, ↓ Aβ accumulation in the anterior cingulate gyrus) [148] MS: • EAE mouse model (effect: reduced spinal cord demyelination, ↓ pro-inflammatory cytokines (IFN-γ, TNF-α, IL−12), ↑ IL−10 (anti-inflammatory), ↓ T-cell proliferation, ↓ cytotoxicity) [149]	[145, 146]

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Table 1 (*continued*)

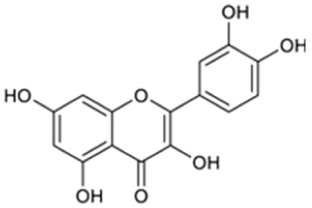
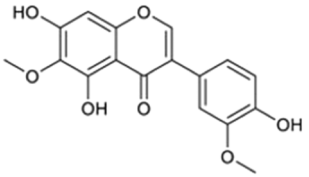
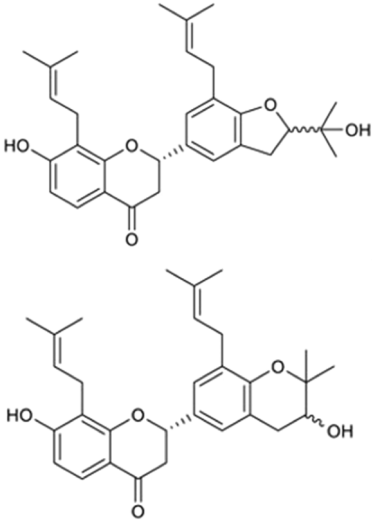
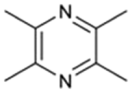
Category	No.	Name	Structure	Source	Research	Refs.
	25	Quercetin		*Medicago sativa* L.	AD: • Aged 3xTg-AD mouse model (effect: ameliorates pathology (Aβ, tau, astrogliosis and microgliosis in the hippocampus and amygdala) and related cognitive deficits) [150] MS: • PBMCs from MS patients (effect: ↓ proliferation PBMCs, ↓ IL−1β, ↓ TNF-α, ↓ MMP−9) [151] • EAE mouse model (effect: inhibited IL−12 signaling pathway (e.g. JAK2/STAT) and Th1 differentiation) [152] Vascular dementia: • Mice exposed to BCAS/CRS (effect: promoting anti-inflammatory microglial phenotype, enhancing myelin debris clearance, reducing neuropsychiatric symptoms such as anxiety and depression) [153]	[154, 155]
	26	Iristectorigenin B		*Belamcanda chinensis*	No direct studies in CNS models	[93, 156]
	27	SPF1 and SPF2		The root of *Sophora tonkinensis* Gagnep.	No direct studies in CNS models	[57, 157]
Alkaloids	28	Tetramethylpyrazine		Medicinal plant *Ligusticum chuanxiong*	ALS: • Clinical trial phase 2 ChiCTR2000039689 (effect: slowed decline in grip strength) [158] MS: • EAE mouse model (effect: decreased demyelination, ↓ pro-inflammatory cytokines IL−18 and IL−17, ↑ anti-inflammatory cytokine IL−10, and ↓ inflammatory infiltration and glial activation) [159]	[160, 161]

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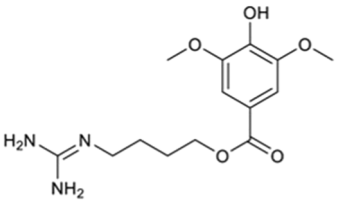
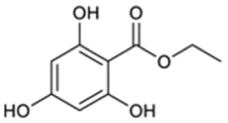
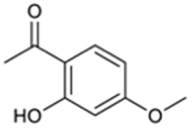
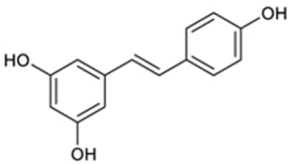
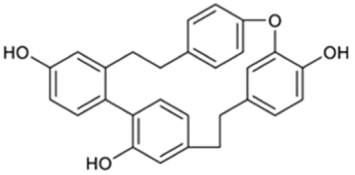
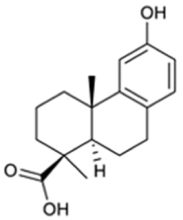
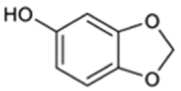
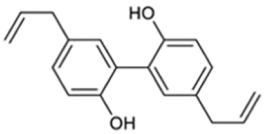
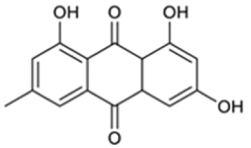
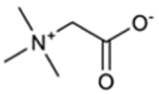
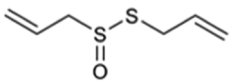
Table 1 (*continued*)

Category	No.	Name	Structure	Source	Research	Refs.
	29	Leonurine		*Herba leonuri*	AD: • Male APP/PS1 mice (effect: improved cognitive function, reduction in hippocampal neuronal damage, ↓ Aβ levels, and reduced oxidative stress) [162]	[163]
Phenol derivatives	30	ETB		*Celtis biondii* Pamp.	No direct studies in CNS models	[164]
	31	Paeonol		*Paeonia suffruticosa*	AD: • APP/PS1 double transgenic mice (effect: ↓ Aβ plaques, ↓ neural loss, inhibited microglial activation and ↓ neuroinflammation, improved learning and memory performance, promoted synaptic plasticity and spine density in hippocampal neurons) [165] ALS: • NSC−34 motor neuron-like ALS cells (effect: improved cell viability against neurotoxicity, ↓ mitochondrial oxidative stress) [166] MS: • CPZ mouse model (effect: improved performance in learning and memory tasks, ↓ oxidative stress and inflammation markers, improved mitochondrial health, prevention of hippocampal MBP loss) [167]	[94, 168]
	32	Resveratrol		Red wine, berries, and peanuts	AD: • Microglial BV−2 cells (effect: blocks gene expression of lipopolysaccharide-derived proinflammatory molecules) [169] • Clinical trial phase 2 NCT01504854 (effect: attenuating the decline of plasma and CSF Aβ40 levels, ↓ CSF TREM2, ↓ MMP−9) [170,171] ALS: • Mouse model TgSOD1-G93A/PGC−1α (effect: improved motor function and survival, ↓ blood glucose levels and ↓ motor neuron loss) [172] MS: • Granulocytes (effect: ↓ ROS production) [173] • EAE mouse model (effect: prevented neuronal loss in eyes) [174] • Clinicial trial IRCT20230315057731N1 (effect: anti-inflammatory and anti-oxidant; ↓ TNF-α, ↓ MDA, ↑ FBS, ↓ HDL levels, no changes in TG levels and fatigue) [175]	[176, 177]
	33	Riccardin C		*Blasia pusilla* L. and *Reboulia hemisphaerica*	No direct studies in CNS models	[178]

(*continued on next page*)

Table 1 (*continued*)

Category	No.	Name	Structure	Source	Research	Refs.
	34	Podocarpic acid		Plant resins	No direct studies in CNS models	[94, 179]
	35	Sesamol		Sesame oil of *Sesamum indicum* L.	AD: • APPswe/PS1dE9 transgenic mice (effect: improved spatial memory, improved neuronal damage, ↓ Aβ accumulation, reduced overexpression of TNF-α and IL−1β) [180]	[181, 182]
	36	Magnolol		*Magnolia officinalis*	AD: • APP/PS1 mouse model (effect: ameliorated cognitive impairment, reduced Ab plaques, inhibited apoptosis) [183] Chronic Cerebral Ischemia: • Oligodendrocytes (effect: promote OL maturation by increased MBP, MAG, PLP1) [184] MS: • EAE mouse model (effect: alleviated disease severity, suppress Th17 cell differentiation and cytokine production) [185]	[186, 187]
	37	Emodin		Traditional Chinese medicines (e.g., *Rheum officinale* Baill.)	AD: • Rats with hyperhomocysteinemia-induced dementia (effect: ↓ Aβ, ↓ tau phosphorylation, ↓ TNF-α, ↓ IL−6) [188] MS: • EAE rat model (effect: reduced body weight loss, alleviated inflammatory cell infiltration and demyelination, decreased expression of inflammatory cytokines and inhibited microglial aggregation and activation, ↓ NLRP3 inflammasome signaling pathway molecules, ↑ SIRT1, ↑ PGC−1α) [189] PD: • MPP+ -induced PD model: ameliorated dopaminergic neuron loss by suppressing iron-dependent cell death and upregulating mitochondrial complex III component UQCRC1) [190]	[191]
Others	38	Betaine		Wheat products, spinach	AD: • Microglial BV2 cells (effect: inhibits amyloid-β42 oligomer-induced neuroinflammation by ↓ IL−1β, IL−18, and TNF-α) [192] • Hyperhomocysteinemic rats (effect: ameliorates AD-like homocysteine-induced memory deficits, ↑ long-term potentiation, and ↑ dendritic branch numbers and density of dendritic spines, attenuated tau phosphorylation and Aß accumulation) [193,194] MS: • CPZ rat model (effect: restored normal myelin structure, ↑ MBP, ↑ balance and motor coordination, ↓ oxidative stress, ↓ IL−4 and IL−17) [195] • EAE mouse model (effect: ↓ symptoms, ↓ leukocyte infiltration, and ↓ demyelination in the CNS) [196]	[197]
	39	Allicin		Garlic	AD: • APP/PS1 double transgenic mice (effect: improved cognition, ↓ Aβ, ↓ oxidative stress, improved mitochondrial dysfunction) [198] SCI: • Sprague-Dawley rats (effect: protected neurons from damage, prevented oxidative stress, inflammatory response and apoptosis, ↑ Nrf2 expression) [199]	[200]

neuroinflammation in RAW264.7 macrophages [110]. Neuroprotection and cell survival are boosted by the interaction of the marine sterol with the TrkB/PI3K/Akt and TrkB/ERK signaling pathways in primary hippocampal rat neurons [206]. Fucosterol can also interfere with AD pathways by inhibiting the β-secretase pathway and inhibiting the formation of Aβ plaques [206]. Besides the Asian brown seaweed *Sargassum fusiforme* (*S. fusiforme*), various European brown seaweeds have been evaluated in the context of AD because of their potency to activate LXRs [84,115,117,118,207]. These seaweeds contained high concentrations of fucosterol, and no hepatic lipogenic side effects were reported in these studies, suggesting either limited activation of LXRα or selective activation [118]. While fucosterol contains structural features associated with LXR activity, such as a conjugated double bond at C24[29], current evidence suggests its LXR agonist activity is weak, making it difficult to definitively categorize it as an effective LXR agonist [84,95,116].

5.2. Oxyphytosterols

Recent research has increasingly focused on 24(S)-saringosterol (Table 1, No. 7), an (auto)oxidation product of fucosterol [86]. This marine oxyphytosterol is present in the Asian brown seaweed *S. fusiforme,* as well as in several European brown seaweeds, including *Himanthalia elongata (H. elongata)* and *Sargassum muticum (S. muticum)* [118]. Although data from the dual-luciferase reporter assay in human cell lines of the liver, monocytes, and colon reported that 24(S)-saringosterol activates both LXRα and LXRβ, others found that 24(S)-saringosterol selectively activated LXRβ, and only LXRα at relatively high concentrations [116,179]. Differences likely stem from the assay type (luciferase activation assay vs receptor binding assay) and cell context [179]. *Martens et al.* have demonstrated that in the context of AD, 24(S)-saringosterol prevents cognitive decline in an APPswePS1ΔE9 mouse model over approximately 3 months [115,116]. 24(S)-saringosterol did not increase triglyceride concentrations in the liver or serum or induce lipogenesis, as evidenced by unchanged gene expression levels of *SREBP-1c* and its target genes, nor did it increase triglyceride concentrations in liver or serum [115]. These findings support the neuroprotective effects of 24(S)-saringosterol, similar to precursor fucosterol, which also exhibits dual neuroprotective and lipid-modulatory effects. Emerging evidence also suggests potential roles of 24(S)-saringosterol in promoting remyelination. In particular, *in vitro* experiments treating OPCs with *H. elongata* lipid extract (rich in 24(S)-saringosterol and fucosterol) suggested early-stage differentiation, as indicated by upregulation of the pre-OL marker O4 [117]. In contrast, treatment with *S. fusiforme* lipid extract did not significantly influence O4 expression [117]. Further research is needed to confirm complete differentiation, utilizing further markers (e.g., MBP, MOG) and to explore the potential of 24(S)-saringosterol, and the brown seaweeds that contain this oxyphytosterol, as a therapeutic option for promoting remyelination in demyelinating diseases. Notably, a recent paper by Zhan *et al.* demonstrated that other oxyphytosterols present in *S. fusiforme*, such as 22-ketocholesterol, can also activate LXRs [86].

22-ketositosterol (Table 1, No. 11), an oxidized derivative of β-sitosterol, also shows promise as a potential therapeutic agent for AD [121]. Unlike its parent compound, 22-ketositosterol exhibits potent LXR agonism due to its carbonyl group at C-22, mimicking the oxidized moieties of endogenous ligands [120]. In mouse models of AD, 22-ketositosterol demonstrates an excellent safety profile, showing no significant adverse effects on liver function or lipid metabolism, even at therapeutic doses. However, further studies are needed to evaluate long-term pharmacodynamics [120].

24-ketocholesterol (Table 1, No. 12), a putative oxidation product of fucosterol, has been identified as an LXR agonist, with evidence of functional activity in SH-SY5Y neuronal cells alongside notable cellular uptake [85]. It upregulates *ABCA1* and *ABCG1* gene expression, and selectively induces *APOE* gene expression in astrocytes, indicating a role in brain cholesterol homeostasis. In HepG2 hepatocytes, 24-ketocholesterol shows low bioavailability due to rapid metabolism [85]. In neurons, 24-ketocholesterol elevates desmosterol while reducing cholesterol and its precursors, suggesting dual regulation of synthesis and efflux. It also induces a threefold increase in CYP46A1. Notably, it selectively induces LXR target genes in neuronal and glial cells, without triggering SREBP–1c–mediated lipogenesis, indicating CNS specificity with minimal hepatic risk [86]. Additionally, two bioactive oxysterols— fucosterol-24,28-epoxide (Table 1, No. 13) and (22E)-3β-hydroxycholesta-5,22-dien-24-one (Table 1, No. 14) —were isolated from *S. fusiforme* and characterized as dual LXRα/β agonists that modulate cholesterol homeostasis genes in a cell-specific manner [86]. Significantly, these marine-derived sterols activated LXR targets without inducing lipogenic genes (*FASN*, *SCD1*, *ACC1*) in hepatocytes, demonstrating their potential as selective LXR modulators [86]. In addition, the stereochemistry of fucosterol-24,28-epoxide, a key intermediate relevant in insect sterol metabolism, whose stereochemistry may provide insights into selective LXR activation, has been explored in earlier studies [208,209].

5.3. Terpenes

The most extensive and varied class of naturally occurring substances is terpenes, often called terpenoids. They are primarily found in plants, and the order and number of isoprene units determine their categorization [210]. Importantly, some terpenes can cross the BBB and are under investigation as potential modulators for LXRs, which may support remyelination in demyelinating diseases [211].

Geraniol (Table 1, No. 15) is an acyclic monoterpene derived from essential oils of aromatic plants [125]. This terpene has been reported to influence lipid metabolism in a manner suggestive of LXRα and Farnesoid X Receptors (FXR) pathway involvement. However, direct activation of these receptors has not yet been fully established [94,125]. FXR and LXR perform complementary and often reciprocal functions in lipid metabolism. In fact, FXR suppresses cholesterol conversion into bile acids via CYP7A1 inhibition, whereas LXR promotes cholesterol efflux and catabolism. Next to FXR and LXR, peroxisome proliferator–activated receptors (PPARs) control genes involved in lipid absorption, excretion, and metabolism. Their coordinated actions are critical to maintaining lipid homeostasis [212,213]. Cineole (Table 1, No. 16) is a small aromatic compound present in teas and herbs and can transactivate both LXR isoforms [93,129]. *Jun et al.* demonstrated that cineole activates both LXR isoforms, upregulating the mRNA expression of LXR-responsive genes *ABCA1* and *ABCG1* [129]. Furthermore, administration of cineole to hepatocytes revealed decreased intracellular lipid accumulation, assessed by Oil Red O staining. The lipid-lowering effect was associated with the absence of LXRα upregulation and concurrent downregulation of the expression of key lipogenic genes, including *SREBP-1c*, *FAS*, and stearoyl coenzyme A desaturase-1 (*SCD-1*) [129]. Thus, cineole is a partial agonist as it reduces cholesterol accumulation by upregulating cholesterol efflux genes while avoiding the side effects of lipid synthesis genes in the liver [93,129]. Another widely studied terpene, acanthoic acid (Table 1, No. 17), a diterpene, has been known for its effect on suppressing the production of inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-6, and monocyte chemoattractant protein-1 (MCP-1) [130]. However, its anti-inflammatory properties may also involve LXR-independent pathways, such as NF-κB signaling inhibition. Although acanthoic acid can activate both LXRα and LXRβ (IC50 = 0,25 μM and 1,49 μM, respectively), it prefers mainly LXRα [93,130]. Still, the potential LXRα-induced side effects associated with LXRα activation remain to be established [93,94,130]. Paeoniflorin (Table 1, No. 19) is a terpene known for its wide range of pharmacological effects, including anti-inflammatory, anti-oxidative, neuroprotective, and immune regulatory properties [133]. Although paeoniflorin modulates lipid metabolism through mechanisms possibly involving LXRα, the liver is protected from undesired side effects, such as hepatic steatosis [94,133].

In particular, the high-fat diet ApoE$^{-/-}$ mice, in which paeoniflorin was administered, prevented the development of the non-alcoholic fatty liver disease (NAFLD)-associated symptoms, such as oxidative stress and liver inflammation [133]. After paeoniflorin administration, the ApoE$^{-/-}$ mice had decreased ROS production, and the mice displayed reduced inflammation markers (e.g., CD68, MCP-1, TNF-α) in the liver, both investigated by fluorescence stainings of liver sections [133]. Altogether, the mentioned terpenes could be interesting plant-based ligands for further investigation regarding LXR activation as a strategy to promote remyelination in demyelinating diseases.

5.4. Flavonoids

The plant's secondary metabolism produces polyphenolic chemicals, which are widely distributed throughout the plant kingdom and defend plants against environmental threats [214]. Polyphenols, and flavonoids in particular, have been hypothesized to have positive health impacts on humans [215]. For example, high consumption of fruits and vegetables high in flavonoids and other polyphenols has been linked in numerous studies to a lower risk and incidence of age-related neurodegenerative diseases [216]. In addition, some flavonoids can pass the BBB and could, therefore, exert their neuroprotective effects directly on brain cells [217].

A well-known flavonoid that regulates cellular lipid metabolism is cyanidin (Table 1, No. 20). This flavonoid can activate both LXR isoforms *in vitro* but has a higher affinity for LXRα compared to LXRβ (EC50 = 3.48 μM and 125.2 μM, respectively) [135]. Cyanidin promotes expression of *ABCA1* and *ABCG5* in macrophages, but it also slightly upregulates *SREBP-1c* expression in hepatocytes (HepG2 cell line), suggesting potential lipogenic side effects [135,136]. In its glycosylated form, cyanidin has been shown to cross the BBB in rats [218,219].

The citrus bioflavonoid hesperetin has been investigated for its potential against atherosclerosis (Table 1, No. 21) [94,139]. It is known for its prominent anti-inflammatory, antioxidant, anti-apoptotic, and lipid-lowering properties [94,139,220]. Moreover, hesperetin has protective effects on the nervous system [221]. Hesperetin has been shown to promote cholesterol efflux, possibly through adenosine monophosphate-activated protein kinase (AMPK) activation and upregulation of LXR target genes [139]. Direct LXRα agonism remains to be confirmed. AMPK activation is an interesting LXR-independent approach for remyelination, as metformin, the activator of AMPK, caused upregulation of neurotrophic factors (e.g., *Bdnf*), recruited OPCs, downregulated *NogoA* (a protein known to inhibit neurite outgrowth), and promoted OL markers (e.g., *Mog*, *Mbp*) in a cuprizone mouse model of MS [222]. Besides, AMPK maintains the balance between anabolic and catabolic pathways for cellular energy homeostasis [223]. Hesperetin can reduce foam cell formation, suggesting potential relevance for atherosclerosis and demyelinating diseases, such as MS and spinal cord injury (SCI) [94,139,224]. Chrysin (Table 1, No. 22) has also been shown to reduce foam cell formation [142].

Two additional flavonoids are quercetin and SPF1/2 (Table 1, Nos. 25 and 27, respectively), with quercetin serving as a pivotal aglycone in

Table 2
Summary of possible remyelinating drugs for each demyelinating disease currently in clinical trials. Based on the data of GlobalData, extracted on the 5th of May 2025. The name of the drug, clinical phase, and company are given for each demyelinating disease.

Disease	Drug name	Clinical phase	Company	Target	ID Clinicaltrials.gov
PPMS	CNMAU−8	Phase III	Clene Nanomedicine Inc	NAD$^+$/NADH [246]	NCT04081714
	Fenebrutinib	Phase III	Genetech USA Inc	BTK in B-cells and myelin cells [247,248]	NCT04544449
	Tolebrutinib	Phase III	Sanofi	BTK in B-cells and myelin cells [247,248]	NCT06372145
	Vidofludimus calcium	Phase II	Immunic Inc	DHODH in activated lymphocytes [249]	NCT03846219
	PTG−007	Phase I	PolTREG SA	CD4 + regulatory T-cells [250]	-
SPMS	Foralumab	Phase III	Tiziana Life Sciences Plc	CD3 receptor on T-cells [251]	NCT06292923
	Frexalimab	Phase III	Sanofi	ICOS of activated T-cells [252]	NCT06141486
	Temelimab	Phase II	GeNeuro SA	HERV-W envelope protein [253]	NCT05049161
	ABA−101	Phase I	Abata Therapeutics	IL−2 pathway of regulatory T-cells [254]	NCT06566261
	Tolebrutinib	Phase III	Sanofi	BTK in B-cells and myelin cells [247,248]	NCT06372145
RRMS	Teriflunomide	Phase I	C GeneTech (Suzhou China) Co Ltd	DHOH in activated lymphocytes [255]	-
	Ocrelizumab biosimilar	Phase I	Amgen Inc	CD20 of B-cells [256]	-
	RNS−60	Phase II	Revalesio Corp	Microglia/macrophage activation [257]	NCT01714089
	Aspirin + dimethyl fumarate	Phase II	Vitalis LLC	NRF2 pathway activation in CNS cells [258]	NCT01156311
	Peginterferon beta−1a	Phase III	Cinnagen Co	IFNAR receptor of immune cells, primarily lymphocytes [259]	NCT05242133
AD	MP−101	IND/CTA filed	Mitochon Pharmaceuticals Inc	Neurons, glial cells (CNS) [260]	-
	BHV−8000	Phase I	Biohaven Ltd	NMDA receptor in neurons [261]	-
	Histamine dihydrochloride	Phase I	AgoneX Biopharmaceuticals Inc	Natural killer cells [262,263]	-
	SIR−2446	Phase I	Sironax Ltd	RIPK1 in cell death and survival [264]	-
ALS	MP−101	IND/CTA filed	Mitochon Pharmaceuticals Inc	Neurons, glial cells (CNS) [260]	-
	NG−1	Phase II	NeuroGenesis Ltd	NGF receptor in neurons [265]	-
	BHV−8000	Phase I	Biohaven Ltd	NMDA receptor in neurons [261]	-
	Histamine dihydrochloride	Phase I	AgoneX Biopharmaceuticals Inc	Natural killer cells [262,263]	-
NMOSD	B−001	Phase III	Shanghai Pharmaceutical Group Co Ltd	CD20 of B-cells [266]	NCT06413654
	BAT-4406F	Phase III	Bio-Thera Solutions Ltd	CD20 of B-cells [267]	NCT06044350
	MIL−62	Phase III	Beijing Mabworks Biotech Co Ltd	CD20 of B-cells [268]	NCT05314010
	Edralbrutinib	Phase II	Jiangsu Hengrui Medicine Co Ltd	BTK in B-cells and myelin cells [247,248]	-
	IMM−0306	Phase II	ImmuneOnco Biopharmaceuticals (Shanghai) Co Ltd	CD20 of B-cells and CD47 [269]	NCT05805943

PPMS; primary progressive multiple sclerosis, SPMS; secondary progressive multiple sclerosis, RRMS; relapsing-remitting multiple sclerosis, AD; Alzheimer's disease, ALS; amyotrophic lateral sclerosis, NMOSD; Neuromyelitis optica spectrum disorders, BTK; Bruton's Tyrosine Kinase, DHODH; Dihydroorotate dehydrogenase, ICOS; Inducible T-cell COStimulator, HERV-W; Human Endogenous Retrovirus-W, IL; interleukin, NRF2; nuclear factor erythroid 2-related factor 2, NMDA; N-methyl-D-aspartate, RIPK1; receptor-interacting protein kinase 1, NGF; neuronal growth factor, -; ID not found.

the plant *Medicago sativa* L. and being the subject of numerous studies highlighting its health benefits [94,225]. Similar to LXR-activation by T09, *Zhang et al.* stated that quercetin stabilizes the *Apoe* levels in mice and reduces Aβ levels in an AD mouse model [46,155]. Therefore, quercetin is hypothesized to exert its function as an activator of LXRs. In the context of atherosclerosis, there are findings that quercetin stimulates the LXR target gene expression *ABCA1*, stimulating the reverse cholesterol pathway [154]. There are already findings about quercetin to be potentially beneficial in remyelination, as it enhances OPC proliferation by activation of the PI3K/Akt signaling pathway for cell survival and proliferation, upregulates genes essential for OPC differentiation (e.g., *MBP* and *Olig2*), and downregulates *Id2* (inhibitor of differentiation) [226,227]. However, direct activation of LXR by quercetin remains unclear, and its role in remyelination may be mediated by other pathways, which remain to be investigated. The flavonoids SPF1 and SPF2 (Table 1, No. 27) displayed similar effects, as they activate LXR and upregulate *ABCA1*, promoting ApoE lipidation [57,228]. Altogether, several flavonoids modulate cholesterol homeostasis and inflammation, with some influencing LXR target genes and others acting through complementary pathways such as AMPK or PI3K/Akt. However, direct LXR agonism is still unclear, and the connection between LXR activation and remyelination for most flavonoids remains to be elucidated.

5.5. Alkaloids

Alkaloids are a large and structurally diverse group of nitrogen-containing secondary metabolites, with over 12,000 identified compounds from various plant species [229]. Two alkaloids with LXR-activating capacity derived from plants are tetramethylpyrazine (Table 1, No. 28) and leonurine (Table 1, No. 29).

Tetramethylpyrazine is one of the active compounds of the dry root of the plant *Ligusticum chuanxiong*. This alkaloid has been shown to upregulate the PPARγ-LXRα-ABCA1 axis, promoting cholesterol efflux and reducing lipid accumulation [161]. Furthermore, tetramethylpyrazine reduces inducible nitric oxide synthase (iNOS) expression, a key mediator of immune activation and inflammation, suggesting neuroprotective potential [160]. The alkaloid is thought not to exert liver side effects, as it reduces *SREBP-1c* expression and lowers inflammation markers in the liver [160]. Leonurine is an alkaloid traditionally utilized for the therapy of menstrual disorders, gynecological disorders, or dysmenorrhea [230]. *Jiang et al.* showed by using an Oil Red O staining that leonurine administration inhibited lipid accumulation and promoted cholesterol efflux in human THP-1 macrophage-derived foam cells [163]. Leonurine also upregulated both mRNA and protein expression levels of ABCA1, ABCG1, PPARγ, and LXRα after administering leonurine to these cells [163]. PPAR can also be an interesting target due to the interconnected roles between LXR and PPAR. Similar to LXR, PPARs can form heterodimers with RXR, resulting in coordinated regulation of gene expression involved in lipid metabolism and inflammation. Their coordinated regulation may be relevant for neuroinflammatory conditions and potentially for remyelination [1,212,231]. Altogether, both tetramethylpyrazine and leonurine enhance the cholesterol transport and reduce inflammation, and in this way, they may support CNS remyelination by improving lipid clearance and modulating neuroinflammatory responses.

5.6. Phenol derivatives

Derivatives of phenol have found industrial applications as chemical reagents, raw materials for producing plastics, and as components of industrial disinfectants [232,233]. Although clinicians were unaware of it, the phenols' potent antibacterial qualities led to the widespread usage of their derivatives as stabilizers and preservatives in an extensive range of medication compositions [234,235]. Currently, phenol derivatives are investigated for their potential anti-inflammatory effects. Certain phenol derivatives have been found to influence cholesterol metabolism, including acting as LXR agonists, and some have demonstrated the capacity to cross the BBB [94,236]. Their ability to cross the BBB and their potential neuroprotective properties make phenol derivatives promising candidates for further research into neuroinflammatory and possibly remyelinating therapies [236].

Ethyl 2,4,6-trihydroxybenzoate, or ETB (Table 1, No. 30), is a phenol derivative studied for its potential cardiovascular benefits due to its cholesterol-lowering effects [164]. Interestingly, *Hoang et al.* demonstrated that ETB modulates LXR activity directly by interacting with the LBD of LXR [164]. This phenol derivative showed similar mechanistic action, but not equal potency, as the pharmacological compound T09 by recruiting the coactivator Trap 220/Drip-2 and D22 [164]. In a macrophage cell line, *Hoang et al.* showed that ETB increased the cholesterol efflux and reduced the cellular cholesterol levels by stimulating the RCT by activating LXRα/LXRβ-responsive transcriptional genes as previously discussed (3. The Functions of LXRs in Remyelination) [94,164].

Traditional Chinese medicine uses paeonol (Table 1, No. 31), a phenolic component extracted from *Paeonia suffruticosa*, to treat inflammatory conditions [168]. In macrophages of ApoE-deficient mice, paeonol increases the mRNA expression of *Abca1* and its protein levels without changing the protein levels of *Abcg1* [168]. According to *Zhao et al.*'s research, this phenolic substance can reduce the production of foamy cells as siRNA-mediated knockdown of LXRα eliminates the paeonol-induced overexpression of *Abca1*, promotes cholesterol efflux, and suppresses cholesterol accumulation, indicating that paeonol may act via an LXRα-dependent mechanism [94,168]. Lastly, emodin (Table 1, No. 36) was investigated for its ability to activate LXR and upregulate LXR-responsive genes in macrophages. Here again, the findings show that emodin activates the PPARγ and LXRα signaling pathway to increase cholesterol efflux from THP1 macrophages [191].

Thus, several phenol derivatives, including ETB, paeonol, and emodin, upregulate LXR target genes and, in this way, enhance cholesterol efflux, suggesting neuroprotective and anti-inflammatory effects. Their modulation of cholesterol metabolism positions them as promising candidates for remyelinating therapies.

5.7. Others

Besides the previous categories of plant-based LXR agonists, other compounds are studied regarding their LXR-activating potency. The first plant-based compound is betaine (Table 1, No. 38), a natural trimethyl glycine in everyday foods such as wheat products and spinach [197]. Betaine is primarily investigated as an LXRα-activating compound. It has been reported to ameliorate lipid accumulation, gluconeogenesis, and inflammation in fructose-fed rats, likely by restoring LXRα and PPARα expression. However, direct receptor activation has not been conclusively demonstrated [197]. Secondly, allicin (Table 1, No. 39), an essential ingredient of garlic, is considered anti-atherosclerotic due to its antioxidant and anti-inflammatory effects [237]. Allicin also induces the upregulation of *ABCA1* in foamy macrophages, likely involving LXRα and PPARγ signaling [200].

6. Remyelinating drugs in clinical trials

Activation of LXRs has been implicated in processes that promote (re)myelination in demyelinating disorders [11]. LXR agonists are promising therapeutic agents due to their central roles in cholesterol metabolism, inflammation, and myelin repair. LXR agonists support myelin repair by promoting the differentiation and maturation of OLs [11,13]. They support remyelination indirectly by promoting cholesterol turnover and recycling (via upregulation of genes such as *ABCA1*, *ABCG1, and APOE*), thereby supplying essential lipids for myelin regeneration and reducing toxic lipid accumulation that impairs myelin repair [12,13]. Besides its indirect effect via cholesterol turnover, LXR

Table 3
Key mechanisms, therapeutic relevance and main challenges of nuclear receptors.

NR	Key Mechanisms in Demyelination	Therapeutic Relevance	Main Challenges
LXR	Modulates lipid and cholesterol metabolism and suppresses inflammation Promotes myelin gene expression and differentiation of OLs [11,46,48,280]	LXR agonists ameliorate EAE and promote remyelination [30,11, 63,64]	Adverse effects such as hepatic steatosis and hypertriglyceridemia [2,65]
PPAR	Modulates lipid and glucose metabolism and inflammation Promotes the synthesis of essential myelin proteins and differentiation of OLs [279,281]	PPAR agonists ameliorate EAE by reducing inflammation and promoting remyelination [279]	Poor solubility across the BBB[282]
RXR	Forms heterodimers with other NRs Enhance CNS remyelination, probably through permissive heterodimerization [283] For more detailed review on RXR, see [24]	RXR agonists alleviate EAE by suppressing inflammation [284, 285] RXR agonists promotes remyelination [286]	Risk of hypothyroidism and elevated blood TG [242, 287]
VDR	Interacts with the active form of vitamin D [288] Modulates calcium homeostasis, cell proliferation, differentiation, and immune responses [289–291] Promotes OL differentiation and myelination [292–294]	Vitamin D deficiency is linked to increased MS risk and cognitive decline [295–299] Vitamin D supplementation reduces demyelination, microglia activation, and macrophage infiltration in the CPZ mouse model [300]	Risk of hypercalcemia [301] Complex ligand-independent, non-genomic and epigenetic effects [302–305]
ER	Regulates cognition, body temperature, and sexual behavior through neuronal modulation [306]	ER agonists alleviate EAE by increasing remyelination [307,308]	Risk of feminization in male patients Potential carcinogenicity [309,310]
PR	Regulates proliferation of neural progenitor cells [311–313] Regulates OPC proliferation and maturation, and increased MBP expression in the cerebellum [314–317]	Progesterone derivatives alleviate EAE via attenuating neuroinflammation and restoring MBP expression [318] Induces polarization of microglia from a pro-inflammatory to anti-inflammatory state [319]	Risk of feminization in male patients Potential carcinogenicity [309,310]
AR	Promotes astrocyte recruitment and myelin regeneration by OL [320]	Testosterone treatment alleviated demyelination in multiple mouse models through the generation of OPCs and mature OL, thereby enhancing the formation of new myelin in the brain [320, 321]	Masculinization in female patients Cardiovascular risk [322,323]
TR	Involvement in OL differentiation and maturation [324–326]	Thyroid hormones administration aids to restore MBP expression and remyelinating OLs in EAE and CPZ-treated demyelinating models [327,328]	Adverse effects such as osteoporosis, increased heart rate and body temperature, and unwanted changes in mood and mental health [329,330]

AR; androgen receptor, BBB; blood brain barrier, CNS; central nervous system, CPZ; cuprizone, EAE; autoimmune encephalomyelitis, ER; estrogen receptor, LXR; liver X receptor, NR; nuclear receptor, OL; oligodendrocyte, PPAR; peroxisome proliferator-activated receptor, PR; progesterone receptor, RXR; retinoid X receptor, TG; triglyceride, TR; thyroid hormone receptor, VDR; vitamin D receptor

agonists also reduce neuroinflammation by repressing pro-inflammatory genes, which aid in myelin debris clearance and facilitate an anti-inflammatory environment favorable for remyelination [12,13].

These mechanisms are relevant across multiple demyelinating and neurodegenerative conditions. In MS, LXRs help support OL survival and lipid recycling during remyelination. In AD, LXR activation in glial cells (e.g., microglia and astrocytes) promotes cholesterol efflux and ApoE lipidation, which may improve myelin stability and reduce neuroinflammation [34,238]. Contrary, in peripheral neuropathies, LXR agonists show that they inhibit the expression of key peripheral myelin genes (e.g., MPZ and PMP22) in Schwann cells and peripheral nerves [45].

Defects in the myelin sheath include hypomyelination (decreased myelin production), dysmyelination (abnormally formed myelin), demyelination (the pathological loss of myelin), and impaired remyelination (inability to repair the loss of myelin) [239]. Neurological diseases caused by demyelination in the CNS range from autoimmune disorders such as MS to genetic disorders such as leukodystrophies and metabolic and toxic causes, including vitamin B12 deficiency and hypoxia [240]. The most commonly described disease associated with demyelination is MS. In this demyelinating disease, primary demyelination is caused by an adaptive immune response of both T and B cells directed against antigens of the CNS or by intrinsic defects within OLs, such as stress, genetic mutations, and aging [241]. In the relapsing-remitting phase of the disease (RRMS), patients suffer from episodic neurological impairment in which demyelination and remyelination alternate. Over time, the episodes develop towards a secondary progressive disability (SPMS). Patients suffer from clinical features such as weakness, sensory loss, visual disturbances, bladder dysfunction, and cognitive problems [18,242]. Eventually, the demyelination and inflammatory damage will result in axonal transection and loss [242]. While MS is the most common demyelinating disorder, other neurodegenerative conditions involving secondary demyelination, such as AD, amyotrophic lateral sclerosis (ALS), neuromyelitis optica spectrum disorder (NMOSD), and spinal cord injury (SCI), could also benefit from remyelinating therapies [16]. Restoring trophic support and protecting neuronal structures by revitalizing OL function, such as through remyelination, offers the potential for treating diseases characterized by neuronal dysfunction and loss [16]. Although demyelination is not a primary characteristic of these conditions, stimulating adaptive myelination can also enhance regeneration [41]. Altogether, there is a need for the development of remyelinating therapies for various neurodegenerative disorders.

Nowadays, for patients with demyelinating disorders, immunotherapies – also called disease-modifying treatments (DMTs) – restrict the activity and availability of immune cells to lower the frequency and severity of new lesions. Although various DMTs are currently licensed for the treatment of demyelinating disorders, they mainly focus on reducing the inflammatory attacks during the disease [243]. Therefore, developing therapies promoting myelin sheath regeneration has become a crucial and promising strategy to delay, prevent, or reverse disease progression [242]. An example of a potential remyelinating therapy is Ponvory, which has been shown to repair cuprizone-induced demyelination and induce OL differentiation [244]. Although Ponvory is

already approved and utilized in RRMS patients, its remyelinating potential is under investigation in a preclinical setting [245]. Other ongoing research also explores potential options to promote remyelination in demyelinating diseases (Table 2). Another strategy could be to combine DMTs with LXR agonists in demyelinating diseases due to their potentially complementary effects in inflammation, cholesterol metabolism and promoting remyelination.

7. Future perspectives for LXR agonists in demyelinating disorders

Current research in remyelinating therapies is often held up by several risks (e.g., limited efficacy, unclear mechanism of action, side effects). Therefore, there is an interest in developing innovative new approaches [18]. Since it is known that (I) perturbation of the CNS cholesterol metabolism is linked to a range of neurodegenerative diseases, (II) cholesterol is released from the damaged myelin and LXRs aid in transporting these particles from astrocytes to OLs and OPCs, (III) myelin debris is cleared by macrophages and phagocytes via LXR activation, and (IV) LXR activation exerts anti-inflammatory effects and upregulates myelin genes (e.g., MBP, PLP), as discussed in 2. Connecting LXRs and Myelin Repair in the CNS and in 3. The Functions of LXRs in Remyelination, the LXR pathway is an interesting pathway for further research regarding the enhancement of remyelination in demyelinating diseases. However, some challenges hinder the clinical translation of LXR agonists that could potentially enhance remyelination:

The challenge of using LXR agonists as potential remyelinating therapy is the LXRα-induced side effects by activating the SREBP-1c pathway in the liver, promoting lipid synthesis, eventually leading to hepatic steatosis and hypertriglyceridemia [118]. To minimize the risk of lipogenic adverse effects, LXRβ-selective or tissue-specific LXR agonists, mimetics of endogenous LXR ligands, or enzymes that increase the concentration of endogenous LXR ligands are researched. The LXRβ-selective pharmacological compounds LXR-623, CS-8080, and BMS-779788 are being investigated, yet have not been successful in clinical trials due to causing unexpected neurological effects as described earlier [69,70]. As the LBD and DBD of both isoforms are very similar, it is challenging to develop these LXRβ-selective compounds [5]. To tackle this challenge, studies already use molecular docking analysis of compounds for their LXRα/β-selective activity by checking the binding affinities and patterns of interaction with amino acids [270]. In addition, virtual screening, such as SwissSimilarity, is used to find new compounds that target LXRα and LXRβ. SwissSimilarity offers a wide range of small-molecule databases suitable for screening purposes. These databases include drugs and clinical candidates, bioactive substances, commercially accessible compounds, and synthetic molecules [270]. Both molecular docking and virtual screening can help discover drugs with selective affinity for specific LXR isoforms, reducing off-target effects.

LXRs are expressed in multiple organs and tissues, contributing to a complex safety profile for LXR agonists. As a result, research has increasingly focused on developing tailored drug delivery systems to enhance tissue specificity. For example, the synthetic agonists GW6340 selectively activates intestinal LXR, while the phytosterol YT-32 has also demonstrated intestine-specific LXR activation [78,271]. Selective activation of LXRs in the CNS remains a challenge, though intranasal or intrathecal administration routes may offer a more CNS-specific delivery method [79,80]. Nanoparticle-based or lipid-based drug carriers are also a promising targeted delivery systems [272,273]. Besides tissue-selective LXR agonists, another strategy involves modulating enzymes involved in the biosynthesis or degradation of endogenous LXR ligands to reduce the risk of side effects associated with synthetic agonists. For example, SH42 has demonstrated to selectively enhance LXR activation in macrophages while avoiding the activation of the lipogenic SREBP-1c pathway in hepatocytes, providing a cell-specific regulation of LXR activity [82].

The natural LXR ligands, oxy(phyto)sterols and other plant-derived compounds offer a promising strategy to activate LXR without inducing adverse side effects. For instance, oxyphytosterols such as 24 (S)-saringosterol and 22-ketositosterol, along with flavonoids like cyanidin, and terpenes such as paeoniflorin, have been shown to activate both LXRα and LXRβ without inducing LXRα-mediated side effects, as they do not stimulate the SREBP-1c pathway [115,120,133,135,136]. Many of these compounds can cross the BBB, essential for exerting therapeutic effects in the CNS [201,211,217]. However, further research using *in vivo* models of demyelination, such as the cuprizone mouse model, is needed to assess their long-term effects on remyelination, as well as their availability, legal restrictions, and extraction feasibility. [272,274]

While LXR agonists have been studied for their neuroprotective and remyelination-promoting effects in the CNS, there is limited direct evidence regarding the impact of LXR antagonists on remyelination. Some studies focus on the ability of LXR antagonists, such as GSK2033[19] and 22(S)-hydroxycholesterol, to induce expression of *ABCD2*, a peroxisomal transporter important for lipid metabolism [275–278]. Since LXR activation has been shown to repress *ABCD2* expression, the use of LXR antagonists leads to an upregulation of *ABCD2* expression [277]. ABCD2, along with other peroxisomal ABC transporters (ABCD1–4) plays a key role in the transport of very-long-chain fatty acids within peroxisomes, making its upregulation potentially beneficial in certain neurodegenerative conditions by reducing oxidative stress and improving lipid metabolism [277,278]. Despite the therapeutic interest in LXR signaling, the role of LXR antagonists remains underexplored. This avenue is particularly relevant given that some LXR agonists have been reported to inhibit peripheral myelin gene expression in Schwann cells via suppression of the Wnt/β-catenin pathway [45]. Furthermore, myelin gene expression in the sciatic nerve was enhanced in LXR KO mice [45]. While such effects are therapeutically undesirable in the context of LXR agonists in demyelinating diseases, they are mechanistically relevant and align with the potential actions of LXR antagonists. These findings suggest that LXR modulation may exhibit tissue- and context-specific effects. Therefore, the underexplored role of LXR antagonists warrants further investigation. Understanding their mechanisms may not only offer alternative therapeutic strategies but also provide insight into the broader effects of LXR signaling in demyelinating diseases.

In addition to LXRs, several other nuclear receptors (NRs) —including PPARs, RXRs, vitamin D receptors (VDRs), estrogen receptors (ERs) progesterone receptors (PRs), androgen receptors (ARs), and thyroid hormone receptors (TRs)—have also been implicated in the treatment of demyelinating diseases (Table 3). These NRs converge on several key mechanisms, such as promoting OL differentiation and attenuating pro-inflammatory immune responses [279]. Despite these shared mechanisms, each receptor presents with its own challenges, such as hepatic steatosis (LXR), poor BBB permeability (PPAR), hypercalcemia (VDR), and hormonal imbalances (ER, PR, AR) (Table 3). These limitations impede clinical translation. Nevertheless, the collective evidence underscores NRs as promising therapeutic targets in demyelinating diseases.

8. Conclusion

While the prospect of LXR activation for remyelination is apparent, considerable challenges remain in turning these LXR-activating compounds into therapeutic applications. Future research should focus on preclinical investigations, clinical trials, and safety assessments for pharmacological and natural LXR agonists. Furthermore, improving tissue-specific targeting techniques and investigating novel drug delivery mechanisms will be critical. By resolving these problems, LXR agonists could become a cornerstone of future remyelination therapies, providing hope to patients suffering from neurodegenerative disorders such as MS and AD.

Table chemical compounds

Chemical compound	PubChem CID
T0901317	447912
GW3965	447905
LXR−623	16734800
CS−8080	16212738
BMS−779788	59251511
YT−32	274520657
GW6340	10231936
WYE−672	46206336
DMHCA	24768125
SH42	145952750

CRediT authorship contribution statement

Jule Richartz: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Sammie C. Yam**: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Na Zhan**: Writing – review & editing. **Melissa Schepers**: Writing – review & editing. **Assia Tiane**: Writing – review & editing. **Monique T. Mulder**: Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Inez Wens**: Writing – review & editing, Supervision, Conceptualization. **Tim Vanmierlo**: Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors have nothing to declare.

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