Current Pharmaceutical Research (CPR)
Vol 1, Issue 2, April-June 2025
Journal Homepage: www.cpr.in

The Expanding Role of Sphingolipids in Liver Fibrosis and Disease Progression

[1]Riya Chandel, [1]Firoz Khan, [1]Taranvirinderdeep Singh*

[1]*School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab.*

Keywords

Sphingolipids, S1P, liver fibrosis, liver disease, NAFLD, MAFLD, sphingosine kinase

Abstract

Sphingolipids, a class of lipids with diverse carbohydrate components, have been increasingly recognized for their role in various diseases, including liver fibrosis and progression of liver disorders. These lipids, particularly sphingosine 1-phosphate (S1P), play a crucial part in liver pathology, contributing to conditions such as steatohepatitis, hepatocarcinogenesis, and ischemia-reperfusion liver injury. S1P is involved in inflammation, immune cell modulation, and fibrosis, which are essential components of non-alcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease (MAFLD). The dysregulation of sphingolipid metabolism, including sphingosine kinase (SphK) activity and its receptors (S1PRs), has been linked to liver fibrosis and cirrhosis. Additionally, sphingolipid accumulation disorders, such as those seen in sphingolipidoses, further underscore the importance of sphingolipid signaling in liver disease progression. Research highlights the potential of targeting the S1P/S1PR pathway for therapeutic interventions in liver fibrosis and other liver-related disorders. As the global prevalence of fatty liver disease rises, understanding the role of sphingolipids in liver function and pathology will be critical for developing effective treatments and management strategies for chronic liver conditions.

***CorrespondingAuthor:**
Taranvirinderdeep Singh (taranvirinder24@gmail.com)

Article Info
Received: 07 May 2025, Received in revised form: 16 June 2025, Accepted: 17 June 2025, Available online: 30 June 2025

ISSN: 3049-2955/Theauthors©2025, under exclusive license to the Sprout Publication
DOI: https://doi.org/10.63785/cpr.2025.1.2.238254

1. Introduction

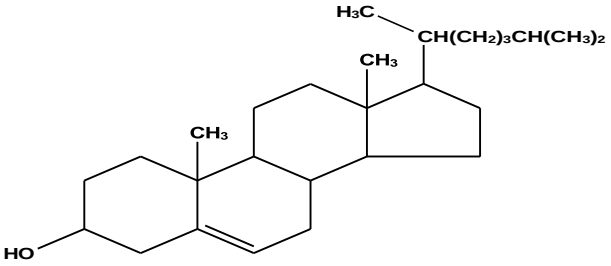
Since their introduction assignment 140 years ago, glycosphingolipids (GSLs) have been found to contain a lipophilic component called ceramide, which can display a wide range of carbohydrate components and have a variable composition [1],[2]. Due to their secretive nature, a bunch of basically shifted lipids known as sphingolipids were to begin with called after the sphinx in the 1870s [3], [4]. They are fundamental parts of the films of all eukaryotic cells. Sphingolipids are presently thought to be involved in oxidative stress, aggravation, autophagy, cell death, and disease states like diabetes, cancer, and multiple sclerosis [5]. One of the most lipid components of cell layers, sphingolipids, plays a part within the cardiovascular, immunological, and neurological frameworks, among other physiological functions [6]. The five S1P receptors (S1PRs) are altered throughout advancement and maturing, as well as in totally different organs. Whereas S1P4 and S1P5 expression is generally constrained to particular cell sorts, S1P1, S1P2, and S1P3 expression is widespread[7]. FTY720 (fingolimod), which was authorized and adopted in 2010 as a standard first-line therapy for relapsing-remitting forms of multiple sclerosis, is one of the chemicals that targets S1P receptors and is of intrigued for the treatment of immune system diseases [8].

GM1 ganglioside accumulation disorder, hexosaminidase A deficiency, Hexosaminidase A and B deficiency variation of GM2-gangliosidosis, Fabry malady, Gaucher illness, metachromatic leukodystrophy, Krabbe malady, Niemann-Pick syndrome malady sort A and B, Farber illness, combined saposin (Sap) insufficiency, SapA insufficiency (Non-classical Krabbe disease), SapB lack (Metachromatic leukodystrophy), and SapC insufficiency (atypical Gaucher malady) are among the more than ten illnesses categorized as sphingolipidoses [9]. Since they were at first isolated from neural tissue, cerebrosides and sphingomyelins got their names [10]. The four essential classes of sphingolipid-binding proteins are transporters,

effectors, proteins, and receptors. Lipids contain greasy acids and cholesterol, which arrange these crucial metabolic functions [11]. Lipid changes within the liver are common as a cause and result of alcoholic hepatitis, non-alcoholic greasy liver infection, steatohepatitis, and chronic hepatitis B and C infection infections[12]. Sphingolipids play a role in hepatocellular function, which propels numerous liver conditions such as hepatocarcinogenesis, steatohepatitis, and ischemia-reperfusion liver injury [14]. Commonly seen causes of hepatic organ sicknesses on a global scale are metabolic-associated fatty liver infection (MAFLD), and within the following decades, its incidence is anticipated to extend [15]. Changes within the extracellular matrix's composition are the essential cause of MAFLD improvement [16]. A bioactive sphingolipid connected to non-alcoholic steatohepatitis (NASH) is sphingosine 1-phosphate (S1P) [17]. Inflammation caused by safe cells could be a major factor in the advancement of NASH [18].

S1P receptors, associated with a collection of five distinct S1P receptor subtypes known as S1P1-S1P5, are expressed suddenly by both innate (macrophages, monocytes, NK, and NKT cells) and adaptive immune cells (T and B lymphocytes) [19]. Even though different intracellular targets of S1P have been recognized, Sphingosine kinases (SphKs) make S1P, and S1P-specific cell surface receptors (S1P1–5) mediate numerous of its functions [20]. A few in vivo and in vitro liver fibrosis models have appeared to benefit from changes in SphKs/S1P/S1P receptor signaling [21]. These days, greasy liver illness is thought to be a prevalent cause of constant liver disease, or may be a developing worldwide health concern [22]. Various liver-related clutters have been connected to sphingolipid metabolic pathways that create sphingosine-1-phosphate (S1P) and its receptor S1P receptors (S1PRs) [23]. Intense liver damage (ALI) may be a condition when the liver is hurt rapidly by substances counting chemicals, liquor, and infections, which harms the liver's cells [24]. A considerable aggregation of extracellular network (ECM) proteins, especially collagen, is indicative of liver fibrosis, a basic arrange within the progression of inveterate liver disarranges toward cirrhosis and possible liver failure [25]. This obsessive condition comes about from maintained liver damage caused by a assortment of insuperable, such as immune system hepatitis, liquor manhandle, metabolic dysfunction-associated steatotic liver illness (MASLD), and constant viral contaminations [26]. Approximately 20 a long time after apoptosis was initially depicted, in 1993, the sphingolipid ceramide was at first associated to this sort of cell death [27].

Lipids are a heterogeneous bunch of compounds, primarily composed of hydrocarbon chains [28]. A lipid is any of the different natural compounds that are insoluble in water [29]. They incorporate fats, waxes, sterols, vitamins, monoglycerides, diglycerides, phospholipids, and others [30].



Sphingolipids, along with glycosphingolipids, are vital in the understanding of a cell's physiology and pathophysiology [31]. Sphingolipids are a subclass of bioactive lipids [32] Sphingolipids, as a member of the class of lipids with a backbone featuring a long-chain amino alcohol, perform structural and signaling functions in the case of eukaryote [33]. The general structure of Sphingolipids - Sphingolipids fall under amphipathic molecules, shallower, they possess both hydrophobic and hydrophilic parts [34]. The hydrophobic region contains the aliphatic chain and long chain attached by amide link at carbon [35]. In hydrophilic portions, the phosphate group, sugar group, or hydroxy group are found [36].

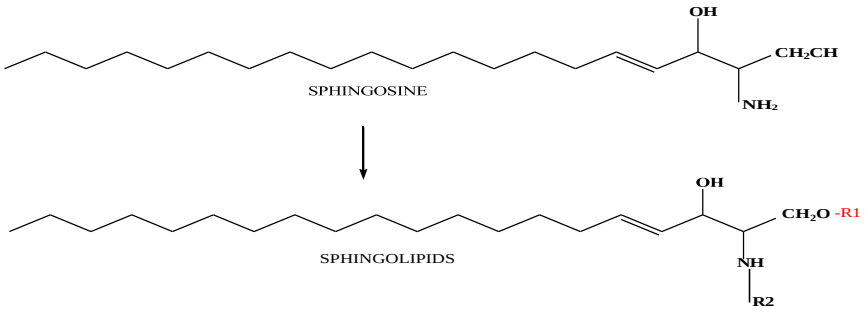


Figure 2: Sphingosine modified to form sphingolipids by addition of R1 and R2 groups.

2. Types of Sphingolipids

Sphingolipid, or more commonly known as glycosphingolipid. Sphingolipids constitute an important part of the cellular membrane and regulate cellular processes such as cell proliferation, differentiation, apoptosis. S1P is essential for an intracellular messenger and extracellular mediator functioning within the organism [37]. Investigations on the influence of SP1/SP3 transcription factors on the activity of the human telomerase reverse transcriptase (hTERT)promoter in the presence of ceramide were conducted in A549 human lung adenocarcinoma cells [38]. Sphingosine, produced by ceramide hydrolysis, is either reused by the salvage pathway or phosphorylated by SphK 1 and 2 in the presence of ATP to yield S1P [39]. S1P can be dephosphorylated within the plasma membrane by lipid phosphate phosphatases (LPP1-3), or cytosolic S1P can be dephosphorylated at the ER due to S1P-specific phosphatases (SPP1 and SPP2) [40].

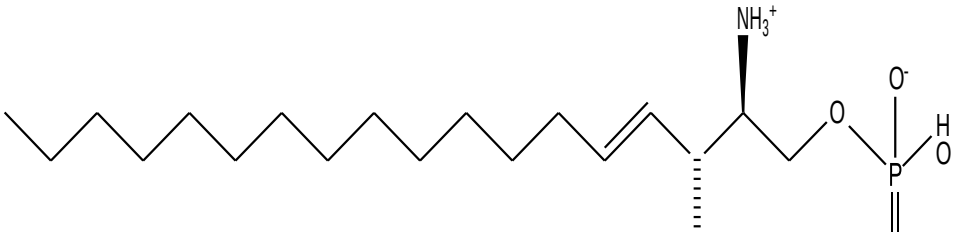
S1P is of significance in the whole human body, it is a key controller of vascular and immune systems, coordinating how immune cells move inside the arterial wall. Besides, it may be of significance to the skin. In the vascular system, S1P controls angiogenesis, vascular stability, and permeability. In the immune system, it is now identified as a key controller of the trafficking of T- and B-cells. S1P interaction with its receptor S1PR1 is required for the exit of immune cells from the lymphoid organs (like the thymus and lymph nodes) to the lymphatic vessels. Blocking of S1P receptors was found to be essential for immunomodulation. S1P has also been found to directly inhibit TLR-mediated immunity from T cells.

Structure of S1P

IUPAC NAME: (2S,3R,4E) -2-amino-3-hydroxyocatdec-4- hydroxyoctadec-4-en-1-yl dihydrogen phosphate

Chemical Formula: C18H38No

Molar Mass: 379.4



2.1. Sphinganine Alkyne

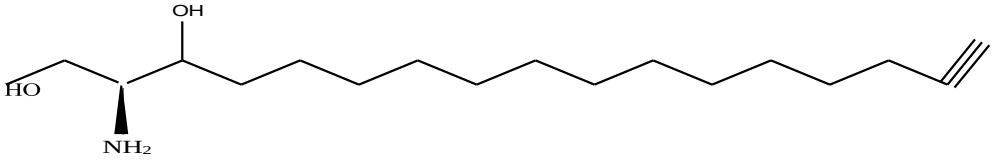


Figure 4: Structure of sphingosine showing a long hydrophobic chain with terminal double bond, and polar groups.

Biological Application: Utilized to examine changes in the bacterial membrane caused by ceramide." 'Click-AT-CLEM` using microscopy to visualize the distribution of azido sphingolipids withinside the Live-cell imaging to observe the incorporation of ceramide into the bacterial membrane the Mammalian immune cell plasma membrane mobileular [41].

Commercial Availability- YES

2.2. Sphinganine Azide

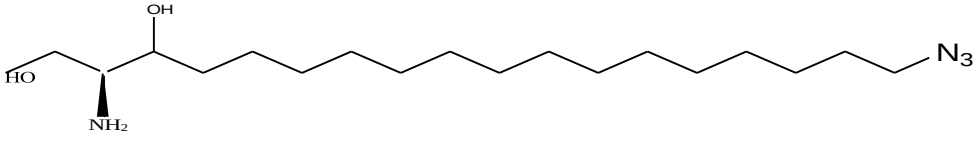


Figure 5: Structure of (2S,3R)-2-amino-3-hydroxy-17-azidoheptadecan-1-ol.

Biological Application: Incubated with rat liver microsomes in vitro and analyzed by mass spectrometry (MS) to identify metabolic modifications induced by enzymes. Immune cells were treated and co-stained with organelle and viral markers to visualize lipid-virus colocalization, followed by dual-color live-cell imaging using fluorescently tagged organellar markers [42].
Commercial Availability- NO

2.3. Sphinganine Azide C14

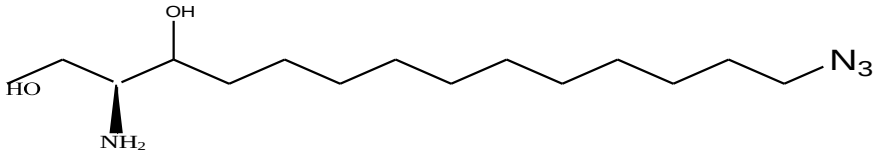


Figure 6: Structure of (2S,3R)-2-amino-3-hydroxy-17-azidoheptadecan-1-ol.

Biological Application: Click' interactions with living cells using diverse dibenzo cyclooctyne tags, lipid extraction, and mass spectrometry on defined pools of samples to elucidate individual azido sphingolipid [41].
Commercial Availability- NO

2.4. Keto-SphinganineazideC14

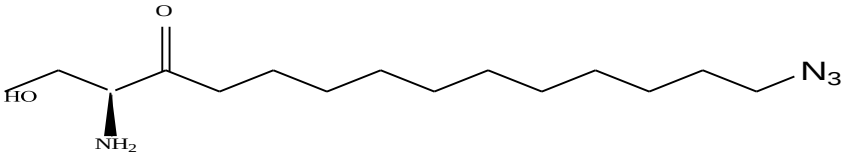


Figure 7: Structure of (2S,3R)-2-amino-3-hydroxy-17-azidoheptadecan-1-ol.

Biological Application: Click' interactions with living cells using diverse dibenzo cyclooctyne tags, lipid extraction, and mass spectrometry on defined pools of samples to elucidate individual azido sphingolipid omes [41].
Commercial Availability- NO

2.5. Deoxysphinganine Alkyne

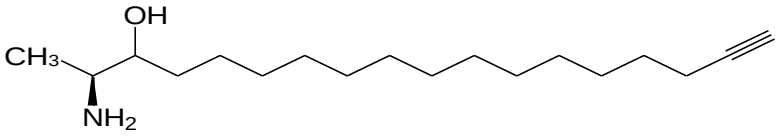


Figure 8: Structure of (2S,3R)-2-amino-3-hydroxy-17-octadecyn-1-ol.

Biological application: Treatment of cells, metabolite analysis, and co-staining of fixed cells with organellar markers to examine trafficking and localization; observation of mitochondrial pathology by co-staining isolated mouse dorsal root ganglion (DRG) neurons were treated with this probe for further analysis [43].
Commercial availability- NO

2.6. Sphingosine Alkyne

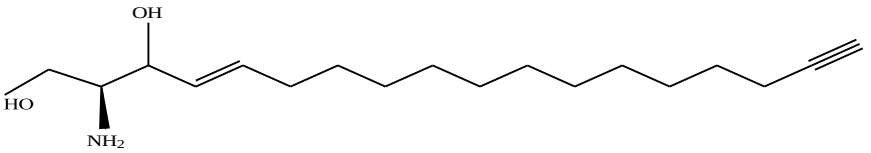


Figure 9: Structure of (2S,3R)-2-amino-3-hydroxy-17-octadecyn-1-ol.

Biological Application: Treatment of cells with TLC for metabolite visualization to study the metabolism of sphingolipids in a viral infection cellular framework; 'fix and click' strategy and Capillary electrophoresis applied to single cells, coupled incorporating Fluorescence-based detection measure differences in sphingolipid metabolism in proliferative and epithelial cells with a differentiated phenotype [44].
Commercial Availability- YES

2.7. ω-N3-Sphingosine

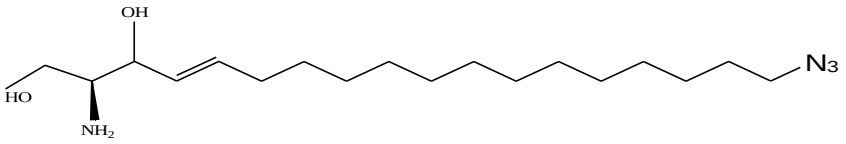


Figure 10: Structure of (2S,3R)-2-amino-3-hydroxy-17-azidoheptadecan-1-ol.

Biological Application: Utilizing click chemistry for bacterial-infected cells, enabling visualization of intracellular sphingosine in fixed cells via actin co-staining and bacterial antibody labelling [45].
Commercial Availability- NO

2.8. 1-N3-Sphingosine

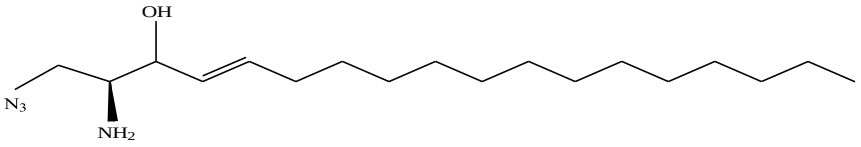


Figure 11: Structure of (2S,3R)-2-amino-3-hydroxy-6-azidooctadec-7-ene.

Biological Application: Click reaction in living cells with bacterial infection was used to investigate the antibacterial effects of sphingosine analogs. This analog is not converted transformed into S1P, as indicated by an in vitro assay with recombinant human SphK [46].
Commercial Availability- NO

2.9. Sphingosine Azide C14

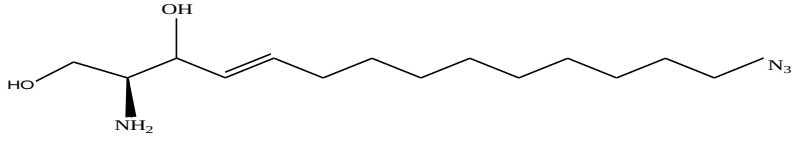


Figure 12: Structure of (2S,3R)-2-amino-3-hydroxy-6-azidooctadec-7-ene.

Biological Application: Employed in click chemistry with different dibenzocyclooctyne labelling in living cells, lipid isolation, concurrent MS analysis of aggregated samples identify individual components azido sphingolipid omens [47].
Commercial Availability- YES

2.10. Pac Sphingosine

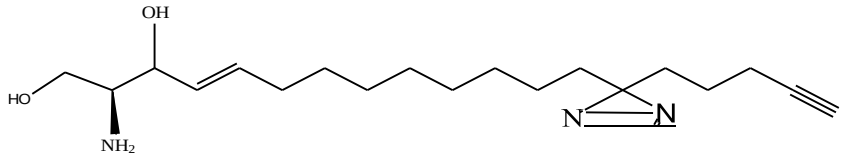


Figure 13: Structure of (2S,3R)-2-amino-3-hydroxy-6-azidooctadec-7-yne.

Biological Application: Rebuilt in liposomes for inside-the-lab link tests with clean proteins; pictures in still metabolic processes in cells study with the use of TLC and MS methods, finding protein content across the cel linkers Via proteomics [48].
Commercial Availability- YES

2.11. Trifunctional Sphingosine

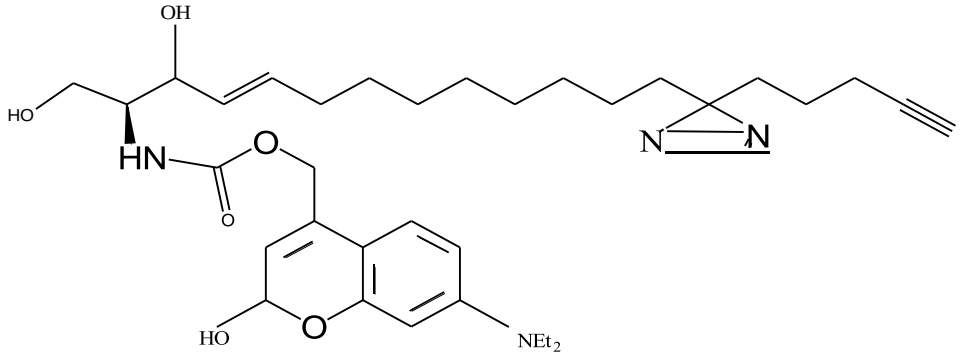


Figure 14: Structure of a dansyl-labeled (2S,3R)-2-amino-3-hydroxy-6-azidooctadec-7-yne derivative.

Biological Application: Solving protein-lipid forces with time detail by protein MS, placing uncaging at the organelle level with a thin light beam used to find the Ca2+ release from lysosomes [49].
Commercial Availability- YES

2.12. Lyso-Pac Sphingosine

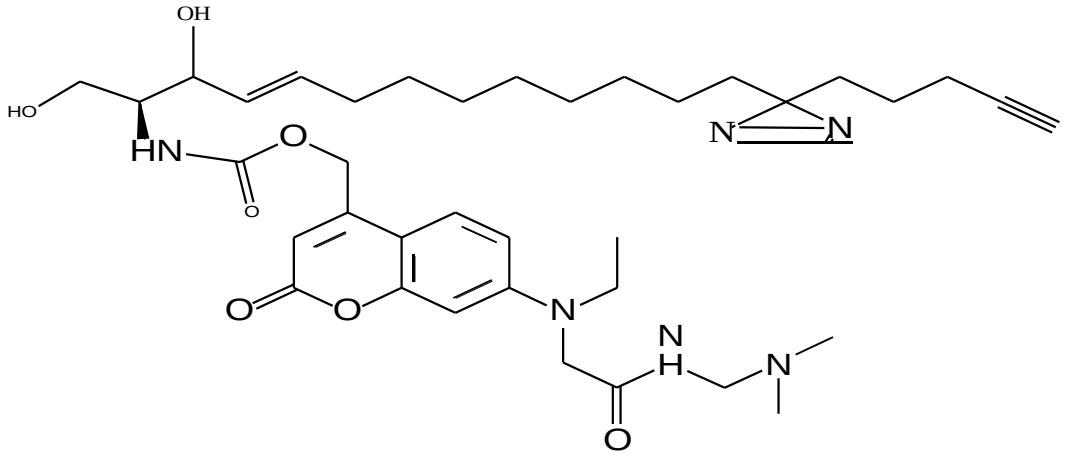


Figure 15: Structure of a dansyl-labeled (2S,3R)-2-amino-3-hydroxy-6-azidooctadec-7-yne derivative.

Biological Application: Focused look at where lipids are in the cell and their movement at specific times; finding out where proteins help lipid interactions, applied in research that looked at how sphingosine moves from the lysosome to the ER [50].
Commercial Availability-NO

2.13. Sphingosine 1-Phosphate Alkyne

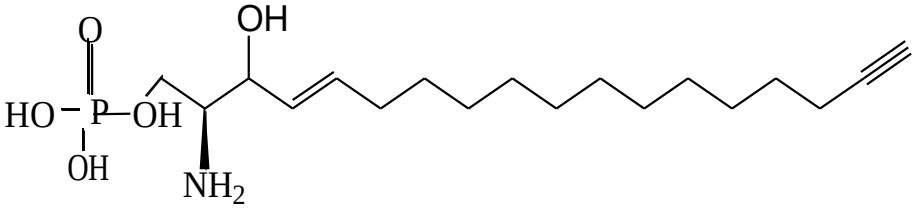


Figure 16: Structure of (2S,3R)-2-amino-3-hydroxy-4-(phosphonooxy) octadec-6-yn-1-ol.

Biological Application: Good for looking at how S1P is made and used, applied in the 'fix and click' method [51].
Commercial Availability-YES

2.14. Sphingosine 1-Phosphate Azide

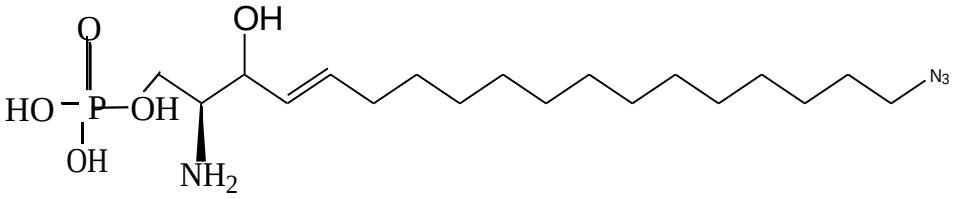


Figure 17: Structure of (2S,3R)-2-amino-3-hydroxy-17-azidoheptadecan-1-ol.

Biological Application: Through live-cell click chemistry to see where S1P is found, and the S1P signaling receptor goes inside cells in culture [52].
Commercial Availability-NO

2.3. How SP is treating NFALD

S1PR2 is a promising prognostic biomarker in the context of Hepatocellular carcinoma in the context of NAFLD (NAFLD-HCC) [53]. S1PR2 was found to be significantly up-regulated using GCDA incorporated in CBAs as a potential treatment for hepatocellular carcinoma (HCC) HCC cells, signal molecules related to the phosphoinositide 3-kinase/AKT/mTOR cascade were also found to be notably up-regulated. This implies that GCDA can elicit the PI3K-AKT-mTOR signaling network through up-regulation of S1PR2 and eventually hepatocellular carcinoma cell activities [54]. It involves lipidomic analysis in plasma and liver in a diet-induced mouse model of NAFLD, across the whole range of histological disease characterization, compared with that from a clinically and histologically well-characterized human cohort of NAFLD patients [55].

S1P upregulated the presence of S1pr4 expression in macrophages and activated the NLRP3 inflammasome using an Inositol trisphosphate and receptor-mediated calcium signaling pathway [56]. Dysregulation of the sphingosine-1-phosphate (SphK1/S1P) signaling pathway contributes to the development of hepatic inflammation and injury [57]. AFLD comprises a spectrum of pathological lesions in the liver, starting with hepatic steatosis with potential progression in up to 20% of patients to hepatic inflammation, cirrhosis, and/her cancer [58]. CER induces cell-type-specific apoptosis primarily through the activation of protein kinase C, protein phosphatases, and proteases , and also modulates the pro-apoptotic Bcl-2-family proteins [59]. Conversely, S1P is an anti-apoptotic factor via inducing the signaling process through G-protein-coupled receptors, resulting in activation of RAS, RAC, protein kinase B, and phospholipase C [60]. FTY720P improved lipid droplet formation, but this improvement was no longer seen in S1PR3, Gq, SREBP, mTOR, PI3K, and PPARγ-inhibited cells, indicating their respective contribution in the process [61]. It is examined the inhibiting effect of CH5169356 on hepatic fibrosis. The in vivo experiment was performed on a male C57BL/6J mouse model. The result of the study showed a decrease in the level of α-SMA and collagen 1A1 by 2.12-fold and 2.5-fold as compared to the untreated group. Overall, the study showed that CH5169356 could inhibit the progression of hepatic fibrosis, showing its potential therapeutic activity [62].

Examined the effect of S1P on Vesicle Trafficking, Wnt/Ca2+, and BMP/Smad Signaling using bone marrow stromal cell lines. The result of the study indicated that Catherine's level was increased upto 5-fold at the dose of 8μM/mL. A further study revealed the EEA1 level was increased upto 5-fold at the dose of 8μM/mL. Further study results showed the level of F-actin was increased upto 10-fold at the dose of 8μM/mL. SFA value is increased in the third and fifth weeks, decreased in the fourth week, and decreased sphinganine-1-phosphate (SA1P in the third week. Ceramide level increased in the fourth and fifth week, while sphingosine (SFO) consistently rose across all time points Sphingosine-1-phosphate (S1P) decreased in the third and fourth weeks, and the S1P/CER ratio decreased in the second, third, and fourth weeks. They examined the influence of HFD intake and oral P. gingivalis (Pg) inoculation on body weight. The difference between HFD+Pg is shown by 1.22, but overall, a very minor difference is shown on the graph. The result of the study showed that higher body weight without imipramine level, but with imipramine value, it increased [63].

The Sphk2 is performed under a high-fat diet regimen and cholic acid. The outcome of the study indicated a reduction in the ND level and an elevation in the level of HFD+CA. The value of the mRNA level for ND is 1, and the value of HFD shown is 2 [64]. Examined that TG/SB3 (Transgenic) mice have levels of CD11b, TNFα, and IL12 expression much higher than those of WT

(Wild Type) mice. CD11 b and TNFα expression levels in TG/SB3 mice are 2.5 times those of WT mice, while IL12 levels are about 4.5 times those of WT mice [65]. It showed that the level of cell death is greater concentrations of PA (palmitic acid) in WT (wild type) and Sphk1-/- (Sphk1 knockout) groups. The Sphk1-/- group always exhibits a greater percentage of cell death than the WT group, suggesting that the lack of Sphk1 enhances cell death upon PA. The cell death percentage is 2 [66].

3. Signalling Pathways of Liver Cirrhosis

3.1. S1P-Driven Signalling in Liver Fibrosis

SphKs take part in the biosynthesis of S1P, and its production is balanced via SPL and S1P phosphatase breakdown activities. SPL can irreversibly degrade the compound [67]. There are five subtypes of S1P receptors (S1PRs), namely S1PR1-5; S1PR1, S1PR2, and S1PR3 are the most broadly demonstrated ones within tissues in a living organism, like liver parenchymal cells and mesenchymal cells [68]. S1PR4 can also be found solely in lymphoid and hematopoietic tissues, and S1PR5 can be found solely in the central nervous system [69]. It has been reported that deregulation of sphingomyelin, ceramide, and S1P backbone correlates with liver disease and liver regenerative processes [70]. Such as liver fibrosis and HCC. This equilibrium may be therapeutically targeted in liver disease. [71]. The pharmacological inhibition of the sphingolipid metabolism pathway could therefore be specifically beneficial for therapeutic purposes in liver regeneration, fibrosis, and HCC, it concludes. [72]. SphK is a prerequisite for activated hepatic stellate cells in generating the cirrhotic liver [73].

TGF-signaling, one of the differentiation processes from HSC to myofibroblast, was found to promote SphK1 expression and result in lowering the levels of ceramide but raising the levels of S-1P [74]. Activation of these receptors may promote fibrosis independently of fibrin generation, through the induction of mediators such as PDGF, CTGF, and MCP-1/CCL2 or the activation of latent TGF-β [75]. SphK1 is also predominantly overexpressed in most solid tumours and points towards a critical involvement in human tumorigenesis [76]. In contrast, SphK2 overexpression arrests Advancement induces cytochrome c-mediated apoptosis and activation of caspase-3 [77]. S1P is produced and released from primary synthetic cells, and in transit, about 60% of S1P associates with apolipoprotein M (ApoM) in high-density lipoprotein (HDL), and 40% of the remaining fraction is bound to albumin [78]. Expression of SphK1 has been found to rise after liver injury, specifically with linkage to Kupffer cells, and attenuation of SphK1 activity reduced mortality in a model of acute liver failure, along with lower markers of liver injury and inflammation [79].

Further, HCC due to NASH is anticipated to increase significantly and become the fastest-growing indication for liver transplant in the United States [80]. During metabolic syndrome, a risk factor for the onset of steatosis, an increase in ceramide and sphingosine-1-phosphate (S1P) has been reported [81]. Ceramide is also involved in liver fibrosis and cirrhosis, cooperating with S1P [73]. Figure 18 Sphingolipid pathway-targeting drugs in liver fibrosis. The figure demonstrated how S1P modulators induce antifibrotic effects by binding to S1PR1-4. Critical enzymes for S1P synthesis pathways, such as SPT and SphK, play significant roles in controlling fibrogenesis. ↑ Represents upregulation, and ↓ represents downregulation. S1P: Sphingosine-1-phosphate; SPT: serine palmitoyl transferase; SphK: sphingosine kinase; TGF-β: transforming growth factor-beta; S1PRs: sphingosine-1-phosphate receptors; CCL2: monocyte chemoattractant protein 1; DMS: N, N-Dimethyl sphingosine; HDAC1/2: histone deacetylase 1 and 2; YAP: yes, associated protein; GTP: guanosine triphosphate; ERK1/2: extracellular signal-regulated kinase [82].

Recent studies, including ours, have shown that activating the notion that pharmacological stimulation of the S1P1 or S1P3 receptors increases adiposity or associated metabolic disease, whereas S1P2's function includes the opposite effect [83]. Additionally, sphingosine kinase (SphK) control of S1P generation is an important factor that affects glucose homeostasis [84].

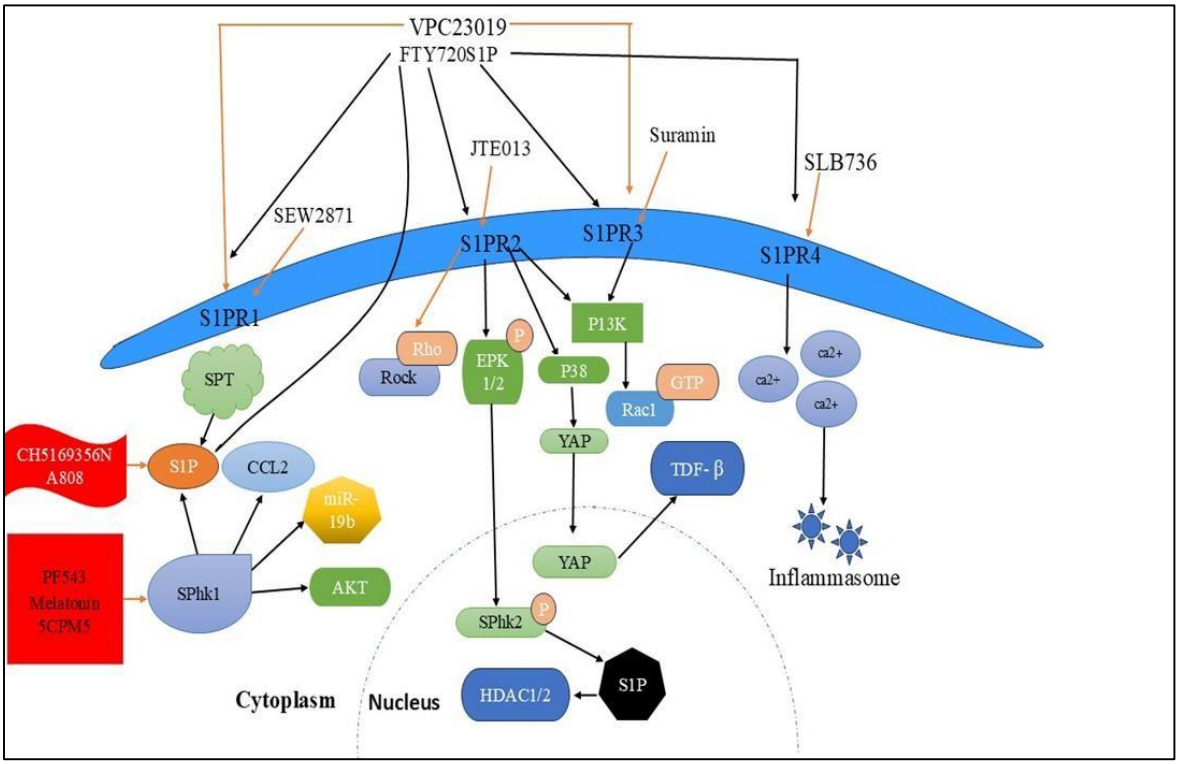


Figure 18: Overview of sphingosine-1-phosphate (S1P) signaling pathways through S1PR1-4 and their pharmacological modulators.

3.2. Mechanism

Direct mechanisms of some of the DMTs, being S1PR modulators, include a concomitant MOA that even restricts the neurodegenerative sequelae [85]. The existing approved DMTs for treatment in MS, as presented through this review article, provide updates and recent evidence on the pharmacological, immunopharmacological, and neuropharmacological properties of the S1PR modulators and, in this article, an emphasis on fingolimod's CNS-oriented, astrocyte-targeting MOA [86].

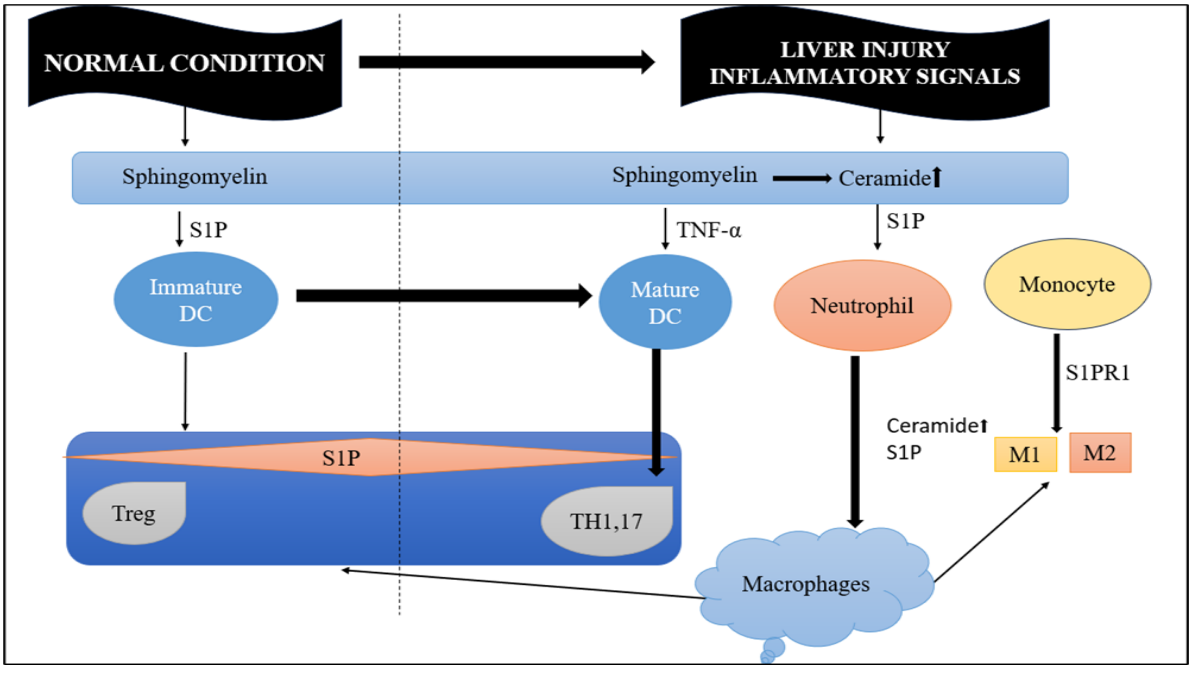


Figure 19: Sphingolipid signalling controls immune cell responses in normal and inflamed liver conditions

3.3. Receptors

Sphingosine1-phosphate (S1P), a metabolite of membrane sphingolipids, controls important

physiological and pathological processes by causing infiltration and activation of multiple cell types via S1P receptors (S1PRs) [87]. The functions of S1P are more complex since there five distinct S1P receptors (S1PRs: S1P1-5) located on the cell surface with modified functions, distinct expression patterns within cells, and imperceptible targets located inside the cell [88]. Current evidence, including that from our group, attests to the interesting idea that Such pharmacological stimulation of S1P1 or S1P3 enhances obesity and related metabolic dysfunctions, but that of S1P2 does the reverse [89]. The mice were given the S1P1,4,5 modulator Etrasimod or the S1P1 modulator Amiselimod, once daily by oral gavage, for the final four weeks of diet administration. Hepatic inflammation or injury became established through histological and gene expression analyses [90].

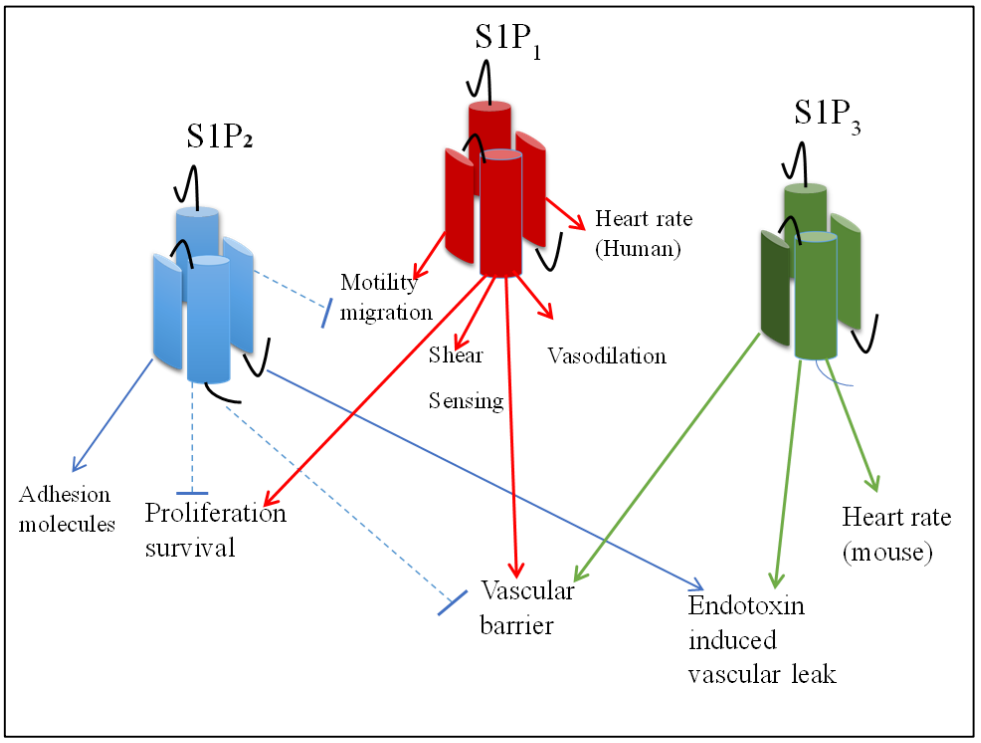


Figure 20: S1P1, S1P2, and S1P3 regulate heart rate, vascular barrier, cell migration, proliferation, and response to vascular injury.

3.4. Diseases

The rate of metabolic dysfunction-related (MASLD) alcoholic fatty liver disease (AFLD), one of the primary etiologies of chronic liver disease, has grown in prevalence with obesity and metabolic disorders, with Altered glucose processing and insulin pathway dysfunction, such as in type 2 diabetes(T2D). Sphingolipids (sphingomyelin, glycolipids, gangliosides) are present in cell membranes, plasma, and lipoproteins [91].

3.5. Metabolism

Metabolism is a biotransformation reaction, in which endogenous as well as exogenous substances are transformed to more polar metabolites to ease their excretion from the body. Metabolism is a process that occurs in 3 phases [92]. Liver impairment can not only decrease the plasma/blood clearance of drugs being removed by hepatic metabolism or excretion via bile, but it may also alter plasma protein binding, and consequently modify the disposition and elimination processes [93]. Portal-systemic shunting, frequent in late-stage hepatic cirrhosis, can heavily reduce systemic of highly extractable drugs after their oral dosing, and consequently result in the extensive rise of the absorption extent [94]. The sphingolipidoses form a group of monogenetic hereditary disorders due to dysfunction of the lysosomal sphingolipid breakdown system, which leads to increased non-degradable storage material accumulation in one or several organs [95]. Steatosis of the liver is primarily a consequence of dysregulation between de novo lipogenesis and fatty acid breakdown, with enhanced free fatty acid influx in the liver [96]. Precursor to ceramide is subsequently oxidized to ceramide catalyzed by dihydroceramide desaturase, which adds a trans-4,5-unsaturation [97]. End-stage liver disease is the last stage of chronic hepatic disease due to various pathogenic factors [98]. Cirrhosis occurs following prolonged inflammation that culminates in the replacement of the normal liver parenchyma with fibrotic tissue and regenerative nodules,

which causes portal hypertension [99]

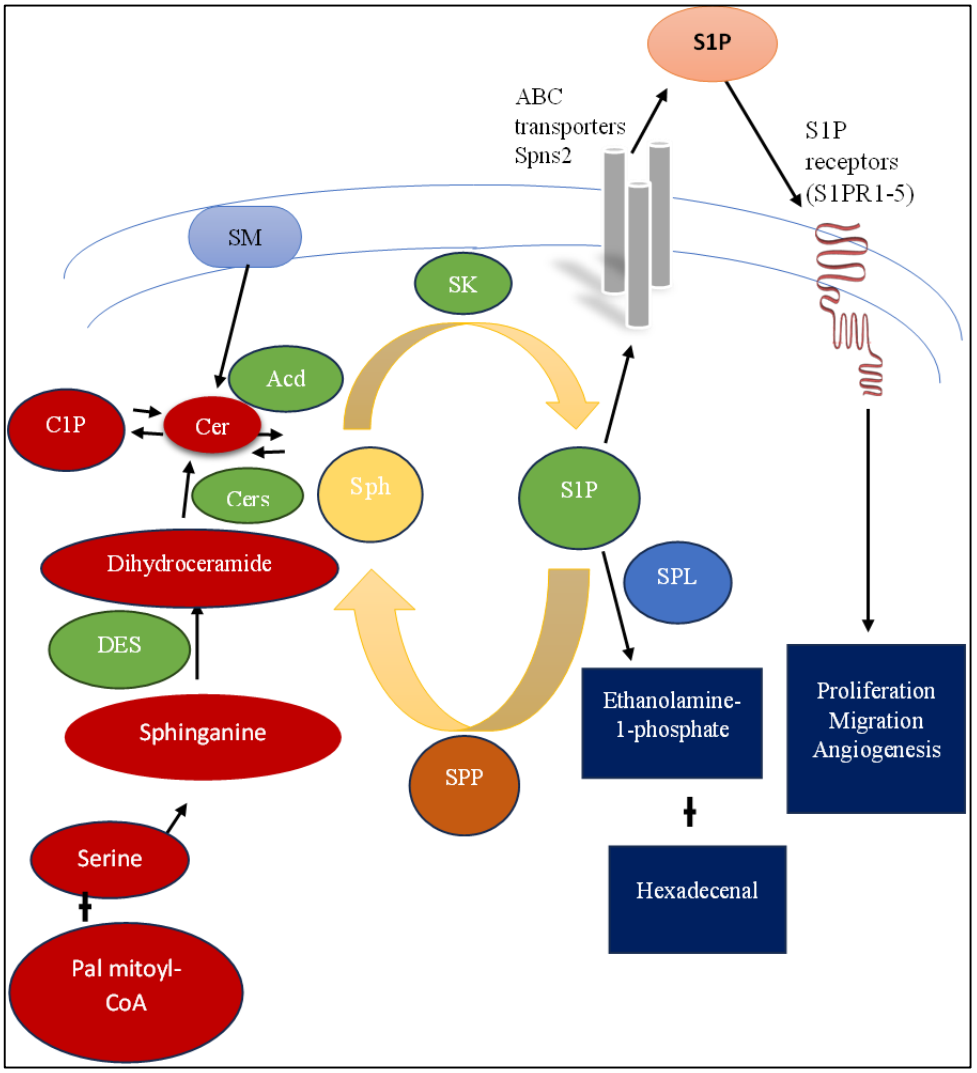


Figure 21: Sphingolipid metabolic pathway leading to S1P production, export, receptor signalling, and its roles in cell proliferation, migration, and angiogenesis.

Liver transplantation is still the sole remedy or treatment for a chosen population of patients, but medication-related interventions having the ability to that can stop the development of decompensated cirrhosis or even reverse cirrhosis are in the process of being developed [100]. Cirrhosis is a rising cause in modern healthcare systems nations, ranking as the 14th main cause of death globally, but fourth in Central Europe [101]. Insulin resistance due to deficiency of insulin receptor substrate-2 (IRS-2)-associated phosphatidylinositol 3-kinase (PI3K) activity results in an accumulation of intracellular fatty acid-derived metabolites like diacylglycerol, fatty acyl CoA, or ceramides [102]. Synchronous metabolic dysregulation, obesity, and allied nutritional derangement can transform the gut microbiota, thus stimulating hepatic and systemic inflammation by directly triggering innate and adaptive immune responses [103]. Platelets have elevated SPHK activity and no S1PL, which enables them to take up massive levels of S1P [104]. Thrombocytes contain SPHK1 as well as SPHK2, but the previous isoform produces 75% of overall SPHK activity [105]. Its frequency is increasing promptly and currently invades approximately 25% of the overall Western population, considering the obesity prevalence [106].

Conclusion

Sphingolipids, including ceramide, sphingosine, and sphingosine-1-phosphate (S1P), are emerging as key modulators of liver pathobiology. Their involvement in critical cellular processes such as inflammation, apoptosis, and fibrogenesis positions them as central players in the

progression of liver fibrosis. Recent studies have highlighted the complex and often cell-type-specific roles of sphingolipids in hepatic injury and repair, suggesting that their dysregulation contributes significantly to the fibrotic cascade. Based on the current evidence, the sphingolipid pathway represents a compelling and novel target for antifibrotic therapeutic development.

Acknowledgment
The authors acknowledge the School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab, for providing the necessary support and resources for the successful completion of this review.

Author Contributions
R.C. Conceptualized the study, F.K. Supervised the review, T.S. Prepared the manuscript draft.

Source of Funding
There is no funding available to conduct this study.

Conflicts of Interest
No conflicts of interest are disclosed by the authors.

References

1. e Ventura, A.E.L., Exploring the biophysical properties of biological membranes: from ceramide domains to lipid droplets. 2023, Universidade de Lisboa (Portugal).
2. Levesque, M.V. and T. Hla, Signal transduction and gene regulation in the endothelium. Cold Spring Harbor perspectives in medicine, 2023. 13(1): p. a041153.
3. Mu, H., et al., Integration of network pharmacology, metabolomics and lipidomics for clarifying the role of sphingolipid metabolism in the treatment of liver cancer by regorafenib. Life Sciences, 2024. 358: p. 123165.
4. Schengrund, C.-L., Sphingolipids: Less Enigmatic but Still Many Questions about the Role (s) of Ceramide in the Synthesis/Function of the Ganglioside Class of Glycosphingolipids. International journal of molecular sciences, 2024. 25(12): p. 6312.
5. Jarocki, M., et al., Lipids associated with autophagy: Mechanisms and therapeutic targets. Cell Death Discovery, 2024. 10(1): p. 460.
6. Kalinichenko, L.S., et al., Sphingolipid control of cognitive functions in health and disease. Progress in lipid research, 2022. 86: p. 101162.
7. Puliti, E., Role of sphingosine 1-phosphate metabolism and signalling in skeletal muscle atrophy and fibrosis. 2022.
8. Ki, S.H., Targeting Acid Ceramidase to Attenuate Kidney Fibrosis. 2022, University of Toronto (Canada).
9. Shaimardanova, A.A., et al., Gene therapy of sphingolipid metabolic disorders. International journal of molecular sciences, 2023. 24(4): p. 3627.
10. Malyarenko, T.V., et al., Sphingolipids of Asteroidea and Holothuroidea: Structures and biological activities. Marine Drugs, 2021. 19(6): p. 330.
11. Aguilera-Romero, A., et al., Impact of sphingolipids on protein membrane trafficking. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 2023. 1868(8): p. 159334.
12. Paul, B., M. Lewinska, and J.B. Andersen, Lipid alterations in chronic liver disease and liver cancer. JHEP reports, 2022. 4(6): p. 100479.
13. Xu, J., et al., Crosstalk between DNA damage repair and metabolic regulation in hematopoietic stem cells. Cells, 2024. 13(9): p. 733.
14. Nojima, H., et al., Critical roles of the sphingolipid metabolic pathway in liver regeneration, hepatocellular carcinoma progression and therapy. Cancers, 2024. 16(5): p. 850.
15. Chan, K.E., et al., Global prevalence and clinical characteristics of metabolic-associated fatty liver disease: a meta-analysis and systematic review of 10 739 607 individuals. The Journal of Clinical Endocrinology & Metabolism, 2022. 107(9): p. 2691-2700.
16. Villesen, I.F., et al., The signalling and functional role of the extracellular matrix in the development of liver fibrosis. Alimentary Pharmacology & Therapeutics, 2020. 52(1): p. 85-97.
17. Jackson, K.G., G.W. Way, and H. Zhou, Bile acids and sphingolipids in non-alcoholic fatty liver disease. Chinese Medical Journal, 2022. 135(10): p. 1163-1171.
18. Huby, T. and E.L. Gautier, Immune cell-mediated features of non-alcoholic steatohepatitis. Nature reviews immunology, 2022. 22(7): p. 429-443.
19. Liao, C.-Y., et al., Modulating sphingosine 1-phosphate receptor signaling skews intrahepatic leukocytes and attenuates murine nonalcoholic steatohepatitis. Frontiers in immunology, 2023. 14: p. 1130184.
20. Wang, P., et al., Roles of sphingosine-1-phosphate signaling in cancer. Cancer cell international, 2019. 19: p. 1-12.

21.
22. Wolska-Gawron, K., et al., Circulating miRNA-181b-5p, miRNA-223-3p, miRNA-210-3p, let 7i-5p, miRNA-21-5p and miRNA-29a-3p in patients with localized scleroderma as potential biomarkers. Scientific reports, 2020. 10(1): p. 20218.
23. Asrani, S.K., et al., Burden of liver diseases in the world. Journal of hepatology, 2019. 70(1): p. 151-171.
24. Tringali, C. and P. Giussani, Ceramide and sphingosine-1-phosphate in neurodegenerative disorders and their potential involvement in therapy. International Journal of Molecular Sciences, 2022. 23(14): p. 7806.
25. Mohammed, N.S., et al., The impact of methamphetamine on liver injury in Iraqi male addicts. Toxicology Reports, 2024. 13: p. 101806.
26. Heyens, L.J., et al., Liver fibrosis in non-alcoholic fatty liver disease: from liver biopsy to non-invasive biomarkers in diagnosis and treatment. Frontiers in medicine, 2021. 8: p. 615978.
27. Choudhury, A., R. Rajaram, and S.K. Sarin, Acute-on-chronic liver failure in metabolic dysfunction-associated fatty liver disease patients: a disease multiplier. Hepatology International, 2024. 18(Suppl 2): p. 941-958.
28. Chung, L.H., et al., Ceramide transfer protein (CERT): An overlooked molecular player in cancer. International journal of molecular sciences, 2021. 22(24): p. 13184.
29. Domínguez, R., et al., Introduction and classification of lipids, in Food Lipids. 2022, Elsevier. p. 1-16.
30. Saini, R.K., et al., Advances in lipid extraction methods—a review. International Journal of Molecular Sciences, 2021. 22(24): p. 13643.
31. Asokapandian, S., S. Sreelakshmi, and G. Rajamanickam, Lipids and oils: an overview. Food biopolymers: Structural, functional and nutraceutical properties, 2021: p. 389-411.
32. Green, C.D., et al., Sphingolipids in metabolic disease: The good, the bad, and the unknown. Cell metabolism, 2021. 33(7): p. 1293-1306.
33. Opalka, L., L. Schlicker, and R. Sandhoff, Sphingolipids. Mass Spectrometry for Lipidomics: Methods and Applications, 2023. 2: p. 425-480.
34. Ali, O. and A. Szabó, Review of eukaryote cellular membrane lipid composition, with special attention to the fatty acids. International journal of molecular sciences, 2023. 24(21): p. 15693.
35. Zhukov, A. and M. Vereshchagin, Polar Glycerolipids and Membrane Lipid Rafts. International Journal of Molecular Sciences, 2024. 25(15): p. 8325.
36. Sun, L., et al., Effect of the Sequence Distribution and Internal Structure on the Hydrophilicity of Poly (ethylene terephthalate-co-aliphatic amide) Copolymers. ACS Applied Polymer Materials, 2022. 4(8): p. 6179-6191.
37. Dai, Y., et al., Hydrolysis of cellulose to glucose in aqueous phase with phosphate group modified hydroxy-rich carbon-based catalyst. Carbon, 2023. 206: p. 72-83.
38. Kundu, D. and K. Halder, Signaling Pathway Governed by Lipid Derived Molecules as Secondary Messenger. International Journal of Advancement in Life Sciences Research, 2024. 7(1): p. 1-14.
39. Garg, A., et al., Current Progress in Targeting Telomere and Telomerase Enzymes for the Treatment of Cancer. Current Cancer Therapy Reviews, 2024. 20(1): p. 26-39.
40. Cirillo, F., et al., The antithetic role of ceramide and sphingosine-1-phosphate in cardiac dysfunction. Journal of cellular physiology, 2021. 236(7): p. 4857-4873.
41. Corsetto, P.A., et al., The critical impact of sphingolipid metabolism in breast cancer progression and drug response. International Journal of Molecular Sciences, 2023. 24(3): p. 2107.
42. Jamecna, D. and D. Höglinger, The use of click chemistry in sphingolipid research. Journal of Cell Science, 2024. 137(6): p. jcs261388.
43. Putlyaeva, L.V. and K.A. Lukyanov, Studying SARS-CoV-2 with fluorescence microscopy. International Journal of Molecular Sciences, 2021. 22(12): p. 6558.
44. Ziegler, C.G.K., Deconstructing cell intrinsic immunity and host-pathogen interactions using single-cell genomics. 2021, Harvard University.
45. Gallion, L.A., Improving the accessibility of chemical cytometry assays for the investigation of sphingosine kinase activity in single cells. 2021, The University of North Carolina at Chapel Hill.
46. de Oliveira Assuncao, M.S., Development of Bio-Instructive Cell-Derived Extracellular Matrix-Based Biomaterials for Wound Healing and Regeneration. 2021, The Chinese University of Hong Kong (Hong Kong).
47. Batliner, M., The\(Candida\)\(albicans\) quorum-sensing molecule farnesol impairs dendritic cell function by modulating the\(de\)\(novo\) synthesis of sphingolipids. 2024, Universität Würzburg.
48. Richter, M., Towards the clinical translation of Extracellular Vesicles–Surface engineering and optimized vesicle-storage. 2021.
49. Chen, P.-H.B., X.-L. Li, and J.M. Baskin, Synthetic Lipid Biology. Chemical Reviews,

50. 2025.
51. Juarez Altuzar, J.M., Development, characterization and application of lysosome-targeted multi-functional sphingosine and cholesterol probes. 2023.
52. Hempelmann, P., et al., The sterol transporter STARD3 transports sphingosine at ER-lysosome contact sites. BioRxiv, 2023.
53. Yao, M., et al., Thin Layer Chromatography Goes Ultrasmall to Assay Sphingosine Kinase Activation in Single Primary Leukemic Cells. Analytical Chemistry, 2025.
54. Laguía, F., et al., Massive endocytosis mechanisms are involved in uptake of HIV-1 particles by monocyte-derived dendritic cells. Frontiers in Immunology, 2025. 15: p. 1505840.
55. Foglia, B., et al., Metabolic reprogramming of HCC: a new microenvironment for immune responses. International Journal of Molecular Sciences, 2023. 24(8): p. 7463.
56. Wang, G., et al., Sphingosine 1-phosphate receptor 2 promotes the onset and progression of non-alcoholic fatty liver disease-related hepatocellular carcinoma through the PI3K/AKT/mTOR pathway. Discover Oncology, 2023. 14(1): p. 4.
57. Cui, X.S., et al., Rodent model of metabolic dysfunction-associated fatty liver disease: a systematic review. Journal of Gastroenterology and Hepatology, 2025. 40(1): p. 48-66.
58. Torres, S., et al., Mitochondria and the NLRP3 inflammasome in alcoholic and nonalcoholic steatohepatitis. Cells, 2022. 11(9): p. 1475.
59. Sun, G., et al., How do sphingosine-1-phosphate affect immune cells to resolve inflammation? Frontiers in Immunology, 2024. 15: p. 1362459.
60. Mansur, N.A.R. and M. Kep, THE UNSEEN BATTLE Living with Non-alcoholic Fatty Liver Disease (NAFLD). 2024: PENERBIT KBM INDONESIA.
61. Liao, J., et al., Mitochondria in brain diseases: Bridging structural-mechanistic insights into precision-targeted therapies. Cell Biomaterials, 2025.
62. Limbu, K.R., et al., Targeting sphingosine 1-phosphate and sphingosine kinases in pancreatic cancer: mechanisms and therapeutic potential. Cancer Cell International, 2024. 24(1): p. 353.
63. Ramos-Molina, B., et al., Therapeutic implications for sphingolipid metabolism in metabolic dysfunction-associated steatohepatitis. Frontiers in endocrinology, 2024. 15: p. 1400961.
64. Hada, N., et al., Novel oral SPT inhibitor CH5169356 inhibits hepatic stellate cell activation and ameliorates hepatic fibrosis in mouse models of non-alcoholic steatohepatitis (NASH). Pharmacology Research & Perspectives, 2023. 11(3): p. e01094.
65. Guo, X., et al., HFD feeding for seven months abolishes STING disruption-driven but not female sex-based protection against hepatic steatosis and inflammation in mice. The Journal of nutritional biochemistry, 2025. 135: p. 109770.
66. Miao, R.R., et al., Intestinal aberrant sphingolipid metabolism shaped-gut microbiome and bile acids metabolome in the development of hepatic steatosis. The FASEB Journal, 2022. 36(8): p. e22398.
67. Novo, E., et al., SerpinB3 as a pro-inflammatory mediator in the progression of experimental non-alcoholic fatty liver disease. Frontiers in immunology, 2022. 13: p. 910526.
68. Qi, Y., et al., Role of sphingosine kinase in type 2 diabetes mellitus. Frontiers in Endocrinology, 2021. 11: p. 627076.
69. Wieczorek, I. and R.P. Strosznajder, Recent insight into the role of sphingosine-1-phosphate lyase in neurodegeneration. International Journal of Molecular Sciences, 2023. 24(7): p. 6180.
70. Cui, M., V. Göbel, and H. Zhang, Uncovering the 'sphinx'of sphingosine 1-phosphate signalling: from cellular events to organ morphogenesis. Biological Reviews, 2022. 97(1): p. 251-272.
71. Fohmann, I., The Role of Sphingosine 1-phosphate and S1PR1-3 in the Pathophysiology of Meningococcal Meningitis. 2024: Bayerische Julius-Maximilians-Universitaet Wuerzburg (Germany).
72. Thiele, M., et al., Sphingolipids are depleted in alcohol-related liver fibrosis. Gastroenterology, 2023. 164(7): p. 1248-1260.
73. Singh, T.P., et al., Gut microbiome as a therapeutic target for liver diseases. Life Sciences, 2023. 322: p. 121685.
74. Ahmed, E.A., et al., Metabolomics and lipidomics screening reveal reprogrammed signaling pathways toward cancer development in non-alcoholic steatohepatitis. International Journal of Molecular Sciences, 2022. 24(1): p. 210.
75. Osawa, Y., et al., Sphingosine-1-phosphate promotes liver fibrosis in metabolic dysfunction-associated steatohepatitis. Plos one, 2024. 19(5): p. e0303296.
76. Fu, F., et al., Role of S1P Signaling Pathway in Pancreatic Diseases. 2024.
77. Humeres, C., H. Venugopal, and N.G. Frangogiannis, The Role of Mechanosensitive

78. Signaling Cascades in Repair and Fibrotic Remodeling of the Infarcted Heart, in Cardiac Mechanobiology in Physiology and Disease. 2023, Springer. p. 61-100.
79. Alkafaas, S.S., et al., The emerging roles of sphingosine 1-phosphate and SphK1 in cancer resistance: a promising therapeutic target. Cancer Cell International, 2024. 24(1): p. 89.
80. Khezri, M.R., S. Mohammadipanah, and M. Ghasemnejad-Berenji, The pharmacological effects of Berberine and its therapeutic potential in different diseases: Role of the phosphatidylinositol 3-kinase/AKT signaling pathway. Phytotherapy Research, 2024. 38(1): p. 349-367.
81. Dietrich, E., Exploring the Interplay between Bile Acids, High-Density Lipoproteins and Endothelial Cells in the Context of Obesity. 2024, University of Zurich.
82. Avni, D., et al., Deletion or inhibition of SphK1 mitigates fulminant hepatic failure by suppressing TNFα-dependent inflammation and apoptosis. The FASEB Journal, 2021. 35(3): p. e21415.
83. Younossi, Z.M., et al., Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clinical Gastroenterology and Hepatology, 2021. 19(3): p. 580-589. e5.
84. Kajita, K., et al., Sphingosine 1-phosphate regulates obesity and glucose homeostasis. International journal of molecular sciences, 2024. 25(2): p. 932.
85. Niranjan, S., B.E. Phillips, and N. Giannoukakis, Uncoupling hepatic insulin resistance–hepatic inflammation to improve insulin sensitivity and to prevent impaired metabolism-associated fatty liver disease in type 2 diabetes. Frontiers in endocrinology, 2023. 14: p. 1193373.
86. Gratpain, V., Siponimod-loaded extracellular vesicles to stimulate remyelination in the central nervous system. 2024, UCL-Université Catholique de Louvain.
87. Phan, F., et al., Sphingosine-1-phosphate signalling in the heart: exploring emerging perspectives in cardiopathology. FEBS letters, 2024. 598(21): p. 2641-2655.
88. Jonnalagadda, D., et al., FTY720 requires vitamin B12-TCN2-CD320 signaling in astrocytes to reduce disease in an animal model of multiple sclerosis. Cell reports, 2023. 42(12).
89. Kohle, F., M.C. Dalakas, and H.C. Lehmann, Repurposing MS immunotherapies for CIDP and other autoimmune neuropathies: unfulfilled promise or efficient strategy? Therapeutic Advances in Neurological Disorders, 2023. 16: p. 17562864221137129.
90. Martín-Hernández, D., et al., Immune System and Brain/Intestinal Barrier Functions in Psychiatric Diseases: Is Sphingosine-1-Phosphate at the Helm? International Journal of Molecular Sciences, 2023. 24(16): p. 12634.
91. Roggeri, A., ROLE OF SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATORS IN MOUSE CENTRAL NERVOUS SYSTEM: RELEVANCE TO AUTOIMMUNE DEMYELINATING DISEASES. 2022.
92. Arosio, B., et al., Sex differences in cardiovascular diseases: a matter of estrogens, ceramides, and sphingosine 1-phosphate. International Journal of Molecular Sciences, 2022. 23(7): p. 4009.
93. Ilhan, I., et al., Cannabidiol mitigates methotrexate-induced hepatic injury via SIRT-1/p53 signaling and mitochondrial pathways: reduces oxidative stress and inflammation. Drug and Chemical Toxicology, 2025. 48(1): p. 210-218.
94. Ogbu, I., E. Ejike-Odeh, and E. Obeagu, Insulin Resistance: A Review. Elite J Lab Med, 2024. 2(3): p. 11-28.
95. Bojić, M., Ž. Debeljak, and F.P. Guengerich, Principles of xenobiotic metabolism (biotransformation), in Pharmacogenomics in clinical practice. 2024, Springer. p. 13-33.
96. De Bruijn, V.r.M., New approach methodologies (NAMs) to understand and predict drug-induced effects on bile acid homeostasis and cholestasis. 2024, Wageningen University and Research.
97. Priya, S., et al., Revolutionizing rheumatoid arthritis treatment with emerging cutaneous drug delivery systems: overcoming the challenges and paving the way forward. Nanoscale, 2025. 17(1): p. 65-87.
98. Scerra, G., et al., Lysosomal positioning diseases: beyond substrate storage. Open biology, 2022. 12(10): p. 220155.
99. Kim, W., et al., Characterization of an in vitro steatosis model simulating activated de novo lipogenesis in MAFLD patients. IScience, 2023. 26(10).
100. Zhao, F., et al., Sphingolipid metabolites involved in the pathogenesis of atherosclerosis: perspectives on sphingolipids in atherosclerosis. Cellular & Molecular Biology Letters, 2025. 30: p. 18.
101. Albillos, A., et al., Cirrhosis-associated immune dysfunction. Nature Reviews Gastroenterology & Hepatology, 2022. 19(2): p. 112-134.
102. Azizan, S.A.F., et al., Chronic Liver Disease: An Updated Review for Healthcare Professionals. Journal of Ecohumanism, 2024. 3(8): p. 13165–13187-13165–13187.
103. Feng, G., et al., Recompensation in cirrhosis: unravelling the evolving natural history of nonalcoholic fatty liver disease. Nature

104. Reviews Gastroenterology & Hepatology, 2024. 21(1): p. 46-56.
105. Guo, Q., et al., Projected epidemiological trends and burden of liver cancer by 2040 based on GBD, CI5plus, and WHO data. Scientific Reports, 2024. 14(1): p. 28131.
106. Engin, A., Nonalcoholic fatty liver disease and staging of hepatic fibrosis. Obesity and Lipotoxicity, 2024: p. 539-574.
107. Bakhru, A., Nutrition and Integrative Medicine for Clinicians: Volume Two. 2023: CRC Press.
108. Chen, P., et al., Metabolic alterations upon SARS-CoV-2 infection and potential therapeutic targets against coronavirus infection. Signal Transduction and Targeted Therapy, 2023. 8(1): p. 237.
109. Kuo, A. and T. Hla, Regulation of cellular and systemic sphingolipid homeostasis. Nature Reviews Molecular Cell Biology, 2024. 25(10): p. 802-821.
110. Murtaza, G., et al., Examining the growing challenge: Prevalence of diabetes in young adults. Medicine International, 2024. 5(1): p. 2.