

Chapter

Perspective Chapter: Targeting PTP1B for the Treatment of Steatosis – Insights from Viscosol's Role in Insulin-Mediated Lipid Metabolism Regulation

Muhammad Asim, Aleena Altaf, Aamir Sohail, Maimoona Arshad, Faiza Noreen, Idrees Raza, Hamza Muneer, Muhammad Murtaza Hasnain, Raza Sufyan and Imran Ullah

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), involves excessive fat buildup in liver cells and is closely linked to insulin resistance, type 2 diabetes mellitus (T2DM), and dyslipidemia. This chapter discusses MASLD pathophysiology, focusing on disrupted lipid metabolism, inflammation, and the key role of protein tyrosine phosphatase 1B (PTP1B) in insulin signaling and metabolic balance. The high-fat diet (HFD) plus low-dose streptozotocin (STZ) mouse model mimics human T2DM and MASLD, showing hyperglycemia, lipid abnormalities, and liver fat accumulation. Viscosol, a flavonoid from *Dodonaea viscosa*, shows strong therapeutic potential as a PTP1B inhibitor. Given at 33 mg/kg intraperitoneally for 7 days, Viscosol improved insulin sensitivity by increasing insulin receptor (INSR), IRS1/2, PI3K, and AKT expression, and regulated lipid metabolism genes (SREBP1c, FAS, PPAR γ). It lowered serum low density lipoprotein (LDL), very low-density lipoprotein (VLDL), and total cholesterol. Histology showed less liver fat, reduced fibrosis markers (α -SMA, TGF- β 1), and decreased inflammation. Viscosol also boosted cholesterol efflux *via* ABCA1 and ApoA1 and lowered inflammatory cytokines (TNF- α , IL-6) and the oxidative stress marker FOXO1, restoring metabolic health. These results suggest Viscosol as a promising natural agent targeting PTP1B to treat insulin resistance, dyslipidemia, and hepatic steatosis in MASLD and T2DM. Further clinical studies are needed to confirm these effects in humans.

Keywords: PTP1B inhibition, MASLD, Viscosol, insulin resistance, dyslipidemia, hepatic steatosis

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive fat accumulation (5–10%) in hepatic cells after excluding other liver disease causes like alcohol use and viral infections [1]. In hepatic steatosis, hepatocytes accumulate triacylglycerol (TAG)-rich lipid droplets, either microvesicular or macrovesicular, without accompanying inflammation or liver damage [2]. Simple steatosis is reversible with lifestyle changes such as diet and increased physical activity [2]. While initial TAG accumulation was thought to be hepatoprotective, excessive intrahepatic fat promotes disease progression [3]. Liver steatosis severity is classified into four grades based on fat percentage in liver cells: Grade 0 (<5%), Grade 1 (5–33%), Grade 2 (34–66%), and Grade 3 (>66%) [4].

1.1 Historical evolution of hepatic steatosis

Addison first described fatty liver in 1836 [5]. Later, similarities were found between liver changes in diabetic and obese patients and those with alcoholic liver disease [5]. In 1980, Ludwig et al. introduced the term nonalcoholic steatohepatitis (NASH) to describe a progressive fatty liver condition resembling alcoholic steatohepatitis [5]. The term “nonalcoholic fatty liver disease” (NAFLD) was coined by Schaffner and Thaler in 1986 [5].

1.2 Transition from NAFLD to MASLD

NAFLD has been redefined as metabolic dysfunction-associated liver disease (MASLD) to better reflect its metabolic basis. There is a bidirectional link between NAFLD and metabolic syndrome, each contributing to the other's development [5]. MASLD diagnosis requires hepatic steatosis plus one or more cardiometabolic risk factors: elevated BMI or waist circumference, impaired glucose metabolism, hypertension, high triglycerides, or low HDL-C [6].

1.3 Role of insulin resistance and dyslipidemia in MASLD

Key contributors to MASLD include obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia, all closely associated with insulin resistance [7, 8]. Peripheral insulin resistance in MASLD and MASH using hyperinsulinemic-euglycemic clamp has been demonstrated [8]. Insulin signaling impairments, especially involving insulin receptor substrate 2 (IRS2), are central to insulin resistance pathogenesis. MASLD rats exhibited increased fasting glucose and insulin, epididymal fat, hepatic steatosis, inflammation, and reduced IRS2 expression compared to controls [8]. Insulin resistance disrupts lipid metabolism, leading to MASLD. Visceral adiposity elevates pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β while reducing adiponectin, causing systemic insulin resistance [9]. Lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL) regulate triglyceride and fatty acid metabolism; LPL hydrolyzes extracellular triglycerides, while HSL breaks down intracellular triglycerides in adipocytes. Insulin resistance increases HSL activity, releasing free fatty acids (FFA). Excess triglyceride storage in skeletal muscle is linked with insulin resistance due to reduced fatty acid oxidation and impaired FFA uptake, increasing serum FFAs [9].

High serum FFAs enter the liver, increasing very low-density lipoprotein (VLDL) production. Insulin resistance elevates FFA influx, reduces apolipoprotein B100 degradation, and increases apolipoprotein CIII expression. Microsomal triglyceride transfer protein (MTP) overexpression also raises VLDL production. SREBP-1c expression is increased, promoting fatty acid synthesis. Hepatic fatty acid metabolism is regulated by uptake, VLDL export, *de novo* synthesis (*via* SREBP-1c), and beta-oxidation. Fat accumulation in the liver is a hallmark of MASLD [8].

1.4 Epidemiology and global burden

MASLD prevalence is rapidly increasing, currently affecting approximately 40% of adults worldwide, projected to reach 55% by 2040. This rise corresponds with a two- to three-fold increase in advanced liver diseases such as cirrhosis, hepatocellular carcinoma, and liver-related mortality. MASLD has surpassed alcoholic liver disease (ALD) as the leading cause of liver cirrhosis and is expected to become the primary cause of liver-related deaths globally [10]. MASLD and T2DM frequently coexist due to shared metabolic and biological pathways. Dyslipidemia, beta-cell dysfunction, and muscle loss significantly contribute to the development of both conditions. MASLD prevalence in T2DM patients ranges between 65% and 70%, reaching over 90% in studies utilizing liver biopsies for diagnosis [10]. NAFLD and NASH negatively affect patient-reported outcomes, including health-related quality of life and work productivity, worsening with disease progression. Patients report higher fatigue, depression, and anxiety compared to healthy populations [11].

1.5 Pathogenesis of hepatic lipid accumulation

1.5.1 Insulin resistance, oxidative stress, and inflammation

Insulin resistance (IR) is a common feature of NAFLD and metabolic syndrome. The two-hit hypothesis posits IR and fat accumulation as the first hit, followed by inflammation, hepatocyte injury, and fibrosis as the second hit, leading to NASH, cirrhosis, and hepatocellular carcinoma [12]. Obesity, a major cause of NAFLD, leads to fat deposition in adipose and hepatic tissue. Elevated FFAs cause lipotoxicity and adipose dysfunction. Dyslipidemia and IR stimulate pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6, which inhibit insulin receptor signaling and reduce hepatic insulin sensitivity, promoting fibrosis and steatosis [12].

Redox reactions maintain hepatic physiological balance but are disturbed by excessive fat accumulation [13].

1.6 Role of *de novo* lipogenesis, mitochondrial dysfunction, and lipid droplet accumulation in hepatocytes

1.6.1 Transition from simple steatosis (NAFLD) to steatohepatitis (MASLD to MASH)

NASH is the progressive form of NAFLD, developing in about 20% of patients. Hepatic steatosis is the initial pathological event and represents the first hit in the double-hit theory, but alone it is insufficient to cause inflammation and fibrosis [14]. Disease progression involves additional factors, including oxidative stress,

genetic variations, dyslipidemia, immune alterations, and gut microbiota changes. Dyslipidemia promotes fatty acid accumulation in the liver, causing steatosis. Oxidative stress, considered the second hit, arises from fatty acid oxidation, generating reactive oxygen species (ROS), lipid peroxidation, DNA damage, mitochondrial dysfunction, and increased pro-inflammatory cytokines. This results in hepatocellular injury, inflammation, and fibrosis [14]. The second hit theory is incomplete; a triple-hit model involving steatosis, lipotoxicity, and inflammation better explains NASH progression. Multiple inflammatory and immune pathways are activated during NASH, including TLR4 binding by free fatty acids, triggering NF- κ B pathway and ER stress, and cytokine production such as TNF- α and IL-1 β . T-cell activation, particularly Th17 and natural killer T cells, also increases in NASH livers [15].

1.7 Molecular mechanism of PTP1B in insulin signaling and insulin resistance

Insulin binding activates its receptor (INSR), leading to phosphorylation of downstream proteins IRS1 and IRS2. This activates the PI3K p85 subunit, which in turn activates AKT (PKB). Activated AKT facilitates GLUT4 vesicle translocation to the cell membrane *via* GTPase RAB10, enhancing insulin action and glucose uptake. Protein tyrosine phosphatase 1B (PTP1B), encoded by the PTPN1 gene (~50 kDa), is expressed in liver, adipose tissue, muscle, and brain. Its expression is upregulated by elevated free fatty acids, ER stress, and inflammatory signals. PTP1B inhibits insulin signaling by dephosphorylating IRS1 and INSR-beta, blocking the PI3K-AKT pathway [16].

1.8 Role of PTP1B in metabolic diseases

PTP1B overexpression reduces GLUT4 receptors on cell membranes, promoting hyperglycemia and contributing to type 2 diabetes. It drives insulin resistance, obesity, and T2DM, which are key factors in MASLD progression. Downregulating PTP1B reduces ER stress and halts MASLD advancement. Additionally, PTP1B overexpression causes leptin resistance, leading to obesity [17]. Human studies show elevated PTP1B protein and gene expression in skeletal muscle, liver, and adipose tissue of diabetic, obese, and insulin-resistant subjects. The PTP1B gene is located at chromosome 20q13, linked to insulin resistance, T2DM, and obesity. PTP1B knockout mice demonstrate resistance to weight gain, improved insulin sensitivity, reduced adipocyte mass, better glucose tolerance, and prevention of beta-cell destruction and diabetes onset [18].

1.9 Therapeutic potential of PTP1B inhibition

PTP1B's critical role in insulin signaling makes it a promising target for T2DM and MASLD therapy. However, challenges in targeting PTP1B include its positively charged active site, poor bioavailability, and selectivity issues. Consequently, few inhibitors reached clinical trials, and many were discontinued due to lack of efficacy [19]. *Dodonaea viscosa* (L.) is a flowering shrub genus with 60 species found in Australia, North America, South Africa, and South Asia. Traditionally, its extracts have been used to treat various diseases [20]. Viscosol contains flavonoids, terpenoids, saponins, phenolics, alkaloids, tannins, and C-alkylated flavonol derivatives. Its main anti-inflammatory compound is hautriwaic acid [20]. *D. viscosa* exhibits antidiabetic properties, confirmed by isolating nine components from Viscosol that inhibit PTP1B [21].

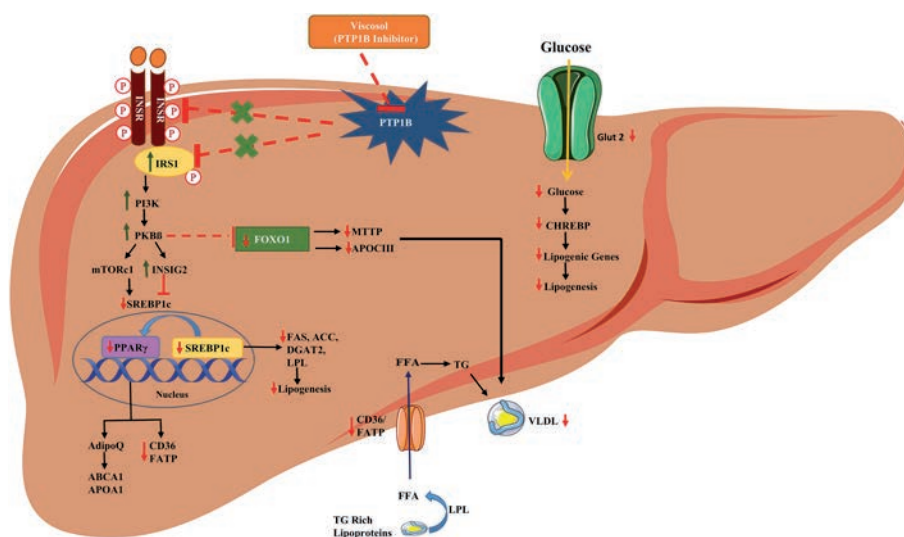


Figure 1.
Proposed molecular mechanism by which Viscosol inhibits PTP1B to improve insulin signaling, reduce lipogenesis, and restore lipid metabolism in MASLD.

As illustrated in **Figure 1**, Viscosol inhibits PTP1B activity, thereby enhancing insulin receptor signaling and downstream pathways that collectively reduce hepatic lipogenesis and improve lipid transport in MASLD (**Figure 1**). Studies report that *D. viscosa* has cytotoxic, anti-inflammatory, antioxidant, antibacterial, antiviral, hepatoprotective, and anti-hyperlipidemic activities [20].

1.10 Objective of this chapter

Since insulin resistance, obesity, and T2DM are root causes of MASLD, down-regulating PTP1B expression can reverse these conditions. Viscosol inhibits PTP1B, thereby potentially reversing MASLD. It upregulates genes involved in glucose uptake and lipoprotein clearance, contributing to dyslipidemia reversal and improvement of hepatic steatosis.

2. Pathophysiology of hepatic steatosis and insulin resistance

2.1 Lipid accumulation and progression of hepatic steatosis

NAFLD is marked by lipid droplet (LD) accumulation in over 5% hepatocytes, known as steatosis. Insulin resistance (IR) drives lipid buildup and disease progression *via* multiple pathways. IR suppresses adipose tissue lipolysis, raising circulating nonesterified fatty acids (NEFAs), which the liver takes up and stores as triglycerides. Hyperinsulinemia stimulates hepatic *de novo* lipogenesis (DNL) through SREBP-1c activation. IR also reduces mitochondrial fatty acid oxidation and VLDL secretion, worsening intracellular fat accumulation [22]. Reactive lipids, such as diacylglycerols (DAG) and ceramides, accumulate, activating PKC ϵ and impairing insulin receptor kinase activity, further disrupting insulin signaling. Lipotoxicity from these intermediates induces oxidative stress and inflammation, advancing steatosis [23].

2.1.1 *De novo* lipogenesis (DNL) and lipid droplet formation

Hepatic steatosis results from both adipose-derived fatty acids and DNL. DNL is transcriptionally regulated and driven by increased glucose uptake and insulin secretion, which upregulate lipogenic genes [24]. Elevated glucose enhances DNL *via* insulin-stimulated SREBP1c and glucose-activated ChREBP. Both enzymes, acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FAS), are essential for fatty acid synthesis. High insulin also suppresses FoxO1, a repressor of SREBP1c and ChREBP, promoting triglyceride storage [25].

Fatty acid oxidation also contributes to steatosis. Normally, mitochondria and peroxisomes perform β -oxidation. Genetic and environmental factors, along with IR, disrupt this process, leading to fat accumulation, microvesicular steatosis, and increased reactive oxygen species (ROS) that damage hepatocytes [26]. PPAR- α , abundant in the liver, regulates genes for fatty acid breakdown. Reduced PPAR- α activity suppresses enzymes, such as ACS, ACADs, and ACAA2, impairing fatty acid oxidation and promoting lipid buildup. This also disrupts carnitine metabolism, vital for mitochondrial fatty acid transport, and worsens oxidative stress by limiting ROS removal [27]. Low PPAR- α correlates with increased fat synthesis and reduced VLDL export, exacerbating NAFLD [28].

2.1.2 *Transition from simple steatosis to steatohepatitis*

Simple steatosis (NAFLD) initially protects hepatocytes by triglyceride storage. However, persistent fat leads to harmful lipid byproducts (DAG, ceramides), causing signaling disruption and oxidative stress. This triggers the release of danger-associated molecular patterns (DAMPs), initiating sterile inflammation [29]. Immune cells, such as Kupffer cells, macrophages, and neutrophils, infiltrate the liver, releasing cytokines (TNF- α , IL-6, MCP-1) that sustain chronic inflammation.

Chronic inflammation activates hepatic stellate cells (HSCs), which differentiate into myofibroblasts, producing excess extracellular matrix proteins. Fibrogenic signals such as TGF- β and Hedgehog molecules from damaged hepatocytes and liver sinusoidal endothelial cells (LSECs) drive fibrosis progression [30].

Fibrosis worsens as impaired autophagy in LSECs causes endothelial dysfunction, elevating NF- κ B inflammatory signaling. This cycle of inflammation and hepatocyte death disrupts liver structure and function. Advanced glycation end products (AGEs) from chronic hyperglycemia bind to their receptor (RAGE) on the liver and immune cells, increasing oxidative stress and fibrosis. These processes collectively drive the shift from simple steatosis to steatohepatitis (NASH) [31].

2.2 Impaired lipoprotein metabolism and dyslipidemia

The liver regulates lipid homeostasis by synthesizing and secreting very low-density lipoproteins (VLDL) that transport triglycerides to tissues. In hepatic steatosis, this balance is disturbed by increased fatty acid delivery from adipose tissue, enhanced *de novo* lipogenesis (DNL), and reduced lipid processing or export *via* β -oxidation and VLDL secretion [32]. As a result, hepatic triglyceride synthesis surpasses VLDL export capacity, causing dyslipidemia characterized by high triglycerides, low HDL cholesterol, and increased small, dense LDL particles [33]. Though VLDL particle number may remain unchanged, their triglyceride content

risks, promoting systemic hypertriglyceridemia and cholesterol-rich LDL formation through intravascular remodeling. Steatosis also impairs HDL metabolism, lowering HDL levels and altering particle size and composition [34].

2.2.1 Disrupted lipoprotein clearance

In hepatic steatosis, triglyceride-rich lipoproteins (TRLs) and remnants clear poorly due to altered receptor-mediated uptake and impaired lipid exchange [34]. Fatty liver cells express fewer LDL receptors (LDLR) because of increased PCSK9, elevating circulating atherogenic LDL [35]. High triglycerides activate cholesterol ester transfer protein (CETP), enriching LDL and HDL with triglycerides. Hepatic lipase then converts these small, dense LDL particles, which more easily penetrate arteries, and small HDL particles that are rapidly cleared by the kidneys, worsening dyslipidemia. Fibrosis in advanced steatosis further disrupts clearance by reducing hepatocyte function to produce VLDL and internalize lipoproteins [34].

2.2.2 Apolipoprotein B100 and microsomal triglyceride transfer protein (MTP)

Apolipoprotein B100 (ApoB100) is the main structural protein of LDL, VLDL, and IDL, essential for lipid transport from the liver to peripheral tissues [36]. MTP transfers triglycerides and phospholipids to ApoB100 during lipoprotein assembly, critical for VLDL formation. Disruption in ApoB100 or MTP leads to hepatic steatosis. MTP overexpression reduces hepatic triglycerides and steatosis [37]. Riboflavin deficiency impairs ApoB100 synthesis, lowering plasma lipoproteins and increasing hepatic lipid storage [38].

2.3 Inflammation, oxidative stress, and insulin resistance

2.3.1 Cytokine-mediated insulin resistance

Pro-inflammatory cytokines, such as TNF- α , IL-6, and MCP-1, released during cell stress, promote insulin resistance. TNF- α induces serine phosphorylation of IRS1, inhibiting its normal tyrosine phosphorylation, and activates JNK and IKK β pathways, increasing oxidative stress and IR [39]. IL-6 upregulates SOCS-3, which blocks insulin receptor and IRS1 phosphorylation. TNF- α also stimulates IL-6, amplifying inflammation [40]. MCP-1 recruits macrophages to adipose tissue, reducing insulin-stimulated glucose uptake and suppressing adipogenic genes GLUT-4 and PPAR- γ , leading to lipotoxicity. It also disrupts hepatic insulin suppression of glucose production, raising hepatic triglycerides and steatosis [41].

2.3.2 JNK-NF- κ B activation and lipotoxicity

Inflammation activates JNK in insulin-sensitive tissues, phosphorylating IRS1/2 at serine/threonine sites, disrupting PI3K-AKT signaling. This reduces GLUT4 translocation and suppresses gluconeogenesis, causing hyperglycemia and hyperinsulinemia. JNK also triggers NF- κ B and AP-1, increasing inflammation and oxidative stress [42]. Mitochondrial dysfunction due to oxidative stress impairs fatty acid breakdown, causing lipotoxicity and increased ROS. ROS-JNK crosstalk promotes lipid peroxidation and ER stress, inducing apoptotic genes and cell death [43]. Persistent JNK and

NF- κ B activation leads to hepatocyte death. DAMPs from dying cells activate hepatic stellate cells (HSCs), increasing collagen and extracellular matrix deposition, promoting fibrosis and, eventually, cirrhosis [44].

2.4 PTP1B: A key regulator in hepatic insulin resistance

Protein tyrosine phosphatase 1B (PTP1B), encoded by PTPN1, is a 50 kDa non-receptor phosphatase regulating multiple signaling pathways including insulin, leptin, and EGF [45]. Tissue-specific effects of PTP1B inhibition are shown in models. Skeletal muscle PTP1B deletion enhances insulin sensitivity by increasing phosphorylation of IR, IRS1, AKT, ERK1/2, and PI3K activity, without affecting lipid profile or adiposity [46]. Adipose-specific deletion increases adipocyte size, leptin, and lipogenesis while maintaining body weight [47]. In the liver, PTP1B deletion improves insulin sensitivity, suppresses gluconeogenesis and lipogenesis, and reduces ER stress by lowering p38-MAPK, JNK phosphorylation, and ER-stress markers PERK and eIF2 α , improving lipid profile without changing body weight or adiposity [48]. **Figure 2** illustrates how overexpression of PTP1B disrupts insulin receptor signaling and glucose uptake, whereas inhibition of PTP1B by Viscosol restores the PI3K-AKT pathway and facilitates GLUT4 translocation, improving insulin sensitivity (**Figure 2**).

2.4.1 PTP1B's effect on insulin receptor and IRS pathway

Normally, insulin binds IR, triggering autophosphorylation and phosphorylation of IRS1/2, activating PI3K. PI3K's regulatory (p85) and catalytic (p110) subunits phosphorylate phosphoinositides, converting PIP₂ to PIP₃. This activates AKT, promoting protein synthesis, survival, and GLUT4 translocation for glucose uptake. PTP1B negatively regulates by dephosphorylating IR, IRS1, and IRS2, dampening PI3K/AKT signaling [49]. **Table 1** summarizes the contrasting roles of PTP1B activation and inhibition on insulin

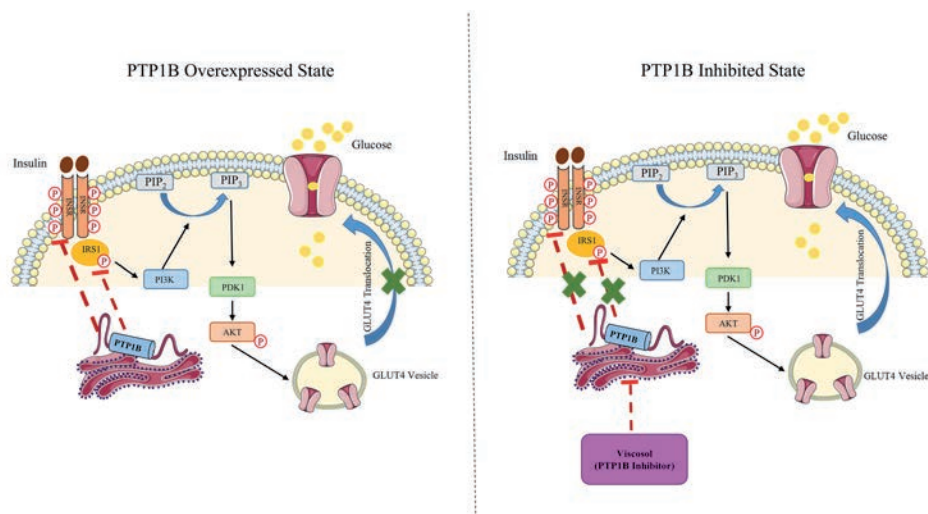


Figure 2. Schematic representation of PTP1B's role in insulin signaling depicting impaired signaling in PTP1B overexpression versus restoration of insulin pathway upon PTP1B inhibition by Viscosol.

Aspect	PTP1B activation	PTP1B inhibition
Insulin signaling	Dephosphorylates insulin receptor (IR) and IRS, leading to insulin resistance.	Enhances insulin sensitivity by maintaining phosphorylation of IR and IRS.
Glucose homeostasis	Impairs insulin-mediated suppression of gluconeogenesis, contributing to hyperglycemia.	Improves glucose uptake, reduces hepatic gluconeogenesis, and lowers blood glucose levels.
Leptin signaling	Dephosphorylates JAK2, leading to leptin resistance and increased food intake.	Enhances leptin sensitivity, reducing food intake, and increasing energy expenditure.
Lipid metabolism	Promotes hepatic lipid accumulation and lipogenesis, contributing to MASLD.	Reduces hepatic fat accumulation by promoting fatty acid oxidation and inhibiting lipogenesis.
Potential therapeutic impact	Worsens metabolic disorders like type 2 diabetes and MASLD.	Shows promise as a target for drug development in insulin resistance, MASLD, and obesity.

Table 1.
Comparison of the metabolic effects and signaling pathways regulated by PTP1B activation versus inhibition.

signaling, glucose homeostasis, leptin sensitivity, lipid metabolism, and their implications for metabolic diseases such as MASLD and type 2 diabetes.

3. Experimental model and methodology

3.1 High-fat diet (HFD)-streptozotocin (STZ) induced diabetic mice model

3.1.1 Model justification

The high-fat diet (HFD) combined with low-dose STZ is a well-established mouse model that closely mimics human T2DM and MASLD. It replicates key features such as persistent hyperglycemia, insulin resistance, dyslipidemia, and hepatic steatosis. Unlike genetic models, this model includes environmental factors such as diet-induced obesity and β -cell damage, allowing better study of metabolic dysfunction and therapeutic testing [50].

3.1.2 Control vs. diabetic groups

Two groups were used: control mice on a standard diet with saline, and diabetic mice fed HFD plus low-dose STZ (40 mg/kg i.p. for 5 days) to impair β -cells. Diabetic mice showed hyperglycemia (>250 mg/dL fasting glucose), raised serum triglycerides, cholesterol, VLDL, LDL, and altered HDL. Histology revealed enlarged adipocytes with bigger lipid droplets, macrophage infiltration, and hepatic steatosis with lipid buildup and hepatocyte dilation [50]. This confirms the model’s validity for T2DM and lipid metabolism studies.

3.2 Viscosol compound: Extraction and administration

3.2.1 Chemical properties and bioavailability

Viscosol (5,7-dihydroxy-3,6-dimethoxy-2-(4-methoxy-3-(3-methylbut-2-enyl)phenyl)-4H-chromen-4-one) is a flavonoid from *Dodonaea viscosa*, traditionally used

for hyperglycemia and lipid disorders [50]. It potently inhibits PTP1B, a negative insulin signaling regulator involved in T2DM. Extraction follows standard phyto-chemical protocols, ensuring purity. Like many flavonoids, Viscosol has poor water solubility and faces metabolic degradation, requiring careful formulation for effective dosing.

3.2.2 Dosage and treatment

Viscosol was given at 33 mg/kg (~1 mg/mouse) *via* intraperitoneal injection dissolved in 1% DMSO. The treatment started after diabetes induction and lasted 7 days, monitoring fasting glucose and lipid profiles. This does align with prior studies showing insulin signaling and lipid metabolism improvements without toxicity [50].

3.3 Key biomarker analysis

3.3.1 Serum lipid profiling

Serum lipids were measured by enzymatic assays: triglycerides, total cholesterol (TC), LDL, VLDL, and HDL. Diabetic mice had high triglycerides, TC, LDL-C, and VLDL-C, with paradoxically raised HDL-C, typical of T2DM dyslipidemia. Viscosol treatment significantly lowered atherogenic lipoproteins and normalized HDL, showing its hypolipidemic effect [50].

3.3.2 Gene expression (RT-qPCR)

RT-qPCR quantified key insulin signaling and lipid metabolism genes in adipose and liver tissues. Targets included INSR, IRS1, IRS2, PI3K, SREBP1c, FAS, and PPAR γ . Viscosol increased INSR, IRS1/2, and PI3K expression, indicating better insulin sensitivity. Lipogenic genes SREBP1c and FAS were up in adipocytes but down in hepatocytes, showing tissue-specific effects that reduce liver fat. PPAR γ was upregulated in adipose, promoting healthy fat cell differentiation [50].

3.3.3 Histology (H&E and Oil Red O)

H&E and Oil Red O staining assessed adipose and liver morphology and lipid accumulation. Controls showed normal cell structure with minimal lipid. Diabetic mice had enlarged adipocytes, increased lipid droplets, macrophage infiltration, and clear hepatic steatosis with disrupted hepatocytes. Viscosol treatment restored normal cell morphology, reduced fat accumulation, confirming its hepatoprotective and anti-steatotic roles [50].

3.4 High-fat diet (HFD)-streptozotocin (STZ) diabetic mice model

3.4.1 Model justification

The HFD combined with the low-dose STZ mouse model replicates T2DM and MASLD well. HFD induces obesity and insulin resistance by fat buildup in the liver and adipose tissue, while STZ selectively damages pancreatic β -cells, reducing insulin secretion. This dual mechanism mimics human T2DM and MASLD effectively, making it ideal for testing treatments [50].

3.4.2 Control vs. diabetic groups

Control mice had a normal diet and saline injections. Diabetic mice on HFD plus STZ showed increased body weight, high fasting glucose, dyslipidemia (high triglycerides, cholesterol, LDL), and hepatic steatosis with enlarged adipocytes and inflammation. These changes mirror human diabetic and liver disease features [50].

3.5 Viscosol compound: Extraction and administration

3.5.1 Chemical properties and bioavailability

Viscosol, a flavonoid from *Dodonaea viscosa*, has strong anti-inflammatory, antidiabetic, and liver-protective effects. It inhibits PTP1B, which negatively affects insulin signaling. Like many flavonoids, it has low solubility and is prone to metabolic breakdown, requiring careful formulation for effective dosing [50].

3.5.2 Dosage and treatment

Viscosol was given intraperitoneally at 33 mg/kg (~1 mg/mouse) for 7 days after diabetes induction. Blood glucose and lipid levels were monitored to evaluate their effect on insulin sensitivity and lipid metabolism [50].

3.6 Key biomarker analysis

Serum lipids were measured enzymatically. Diabetic mice had high triglycerides, total cholesterol, LDL, and VLDL, with altered HDL. Viscosol treatment lowered these atherogenic lipids and normalized HDL, showing improved lipid metabolism [50].

3.6.1 Gene expression (RT-qPCR)

RT-qPCR assessed insulin signaling and lipid metabolism genes in adipose and liver tissues. Viscosol increased INSR, IRS1/2, PI3K, and AKT expression, improving insulin sensitivity. Lipogenic genes (SREBP1c, FAS, ACC) decreased in the liver but increased in adipose tissue, suggesting better lipid balance. PPAR γ was upregulated in adipose, supporting healthy fat cell function [50]. Histology showed normal adipocytes and liver controls. Diabetic mice had enlarged fat cells, lipid droplets, macrophage infiltration, and liver steatosis with disrupted hepatocytes. Viscosol treatment reduced fat buildup and inflammation, restoring normal tissue structure, confirming its protective role [50].

4. Results and findings

4.1 Improvement in lipid profile and reduction in hepatic steatosis

4.1.1 Lipid biomarker changes

Treatment with Viscosol significantly improved serum lipid profiles in HFD-STZ diabetic mice. Levels of LDL, VLDL, and total cholesterol were notably reduced compared

to untreated diabetic controls [50]. This lipid-lowering effect supports better insulin signaling and lipid metabolism, as shown by gene expression and histology data [50, 51]. These changes help reduce cardiovascular risks commonly seen in diabetes.

4.1.2 Cholesterol efflux enhancement

Viscosol also enhanced cholesterol efflux by increasing the expression of ABCA1 and ApoA1, key proteins involved in transporting cholesterol to HDL particles [51]. This improves reverse cholesterol transport, protecting cells from lipid toxicity and reducing atherosclerosis risk.

4.2 Histological changes in liver and adipose tissue

Histological analysis (H&E and Oil Red O staining) showed that Viscosol lowered lipid droplet accumulation in liver tissues. Diabetic mice had severe steatosis and disrupted liver cell structure, but treatment reduced fat buildup and improved liver morphology [50]. This aligns with its effect on genes regulating lipid metabolism.

Viscosol treatment also decreased fibrosis and inflammation markers like α -SMA and TGF- β 1, leading to improved liver function tests (ALT, AST) [50, 51]. This confirms its protective effect against liver damage related to steatohepatitis and diabetes.

4.3 PTP1B inhibition restores insulin sensitivity

At the molecular level, Viscosol inhibited PTP1B, a negative regulator of insulin signaling. Expression of insulin receptor (INSR), IRS1, IRS2, PI3K, and AKT increased, improving glucose uptake and lowering blood glucose [50, 51]. This highlights the therapeutic potential of targeting PTP1B in insulin resistance. Chronic inflammation and oxidative stress contribute to insulin resistance. Viscosol significantly reduced pro-inflammatory cytokines TNF- α , IL-6, and oxidative stress marker FOXO1 in liver and adipose tissue [51]. This reduces inflammation, improves insulin sensitivity, and prevents tissue damage and fibrosis.

5. Synergy between Viscosol and GLP-1

The synergy between Viscosol (endoscopic gastric remodeling, EGR) and GLP-1 receptor agonists (GLP-1RA) comes from their combined effects on weight loss and liver health in MASLD patients with advanced fibrosis. EGR reduces stomach size, limits food intake, and slows digestion, while GLP-1RAs lower appetite, improve insulin sensitivity, and delay gastric emptying [52]. Together, they provide better weight reduction, improved liver fibrosis markers, and reduced insulin resistance than either alone. This combination offers an effective, less invasive treatment for complex metabolic liver disease cases.

5.1 Role of metformin in treating MASLD

Metformin improves insulin sensitivity, reduces liver glucose production, and modulates lipid metabolism. It activates AMPK, which lowers liver fat by blocking lipogenesis and increasing fatty acid oxidation. Metformin also reduces liver enzymes (ALT, AST), signaling less inflammation, and increases gut hormones like GLP-1 and

GDF15 that control appetite and metabolism [52]. It benefits gut microbiota, promoting metabolic health. Though histological improvements such as fibrosis reversal remain inconsistent, metformin is a cost-effective MASLD treatment, especially combined with drugs like GLP-1RAs.

5.2 SGLT2 inhibitor role in MASLD treatment

Originally for T2DM, SGLT2 inhibitors show promise in MASLD by enhancing insulin sensitivity and lowering blood glucose, thus preventing liver fat buildup. They also reduce liver inflammation and may slow fibrosis progression that leads to cirrhosis [52]. Their cardiovascular benefits are critical since MASLD increases heart disease risk. Although not yet officially approved for MASLD, early data suggest SGLT2 inhibitors could be valuable alongside standard liver therapies. **Table 2** highlights the clinical, pathological, and therapeutic differences between MASLD and MASH, emphasizing their progression from simple steatosis to inflammatory and fibrotic liver disease.

6. Advanced drug delivery systems using nanotechnology

6.1 Lipid-based nanoparticles

Micelles, liposomes, and lipid nanoparticles (LNPs) are favored for drug delivery due to biocompatibility and flexibility. Micelles effectively deliver hydrophobic drugs, liposomes carry both hydrophilic and hydrophobic agents, and LNPs protect nucleic acids with controlled release, critical for mRNA vaccines [53–55].

6.2 Polymeric drug delivery systems

Made from biodegradable polymers (PLGA, PLA, PEG), these nanoparticles allow controlled drug release. They can respond to stimuli like pH or reactive oxygen

Feature	MASLD (NASLD)	MASH (NASH)
Definition	Excess liver fat (≥5% of hepatocytes) without significant alcohol consumption.	Liver fat accumulated with inflammation and hepatocyte injury (ballooning), with or without fibrosis.
Pathogenesis	Insulin resistance, dyslipidemia, and metabolic dysfunction drive hepatic steatosis.	Chronic inflammation leads to hepatocyte damage, fibrosis, and potential progression to cirrhosis.
Histological features	Macro vesicular steatosis without significant inflammation or fibrosis.	Steatosis with hepatocyte ballooning, lobular inflammation, and fibrosis.
Metabolic associations	Strongly linked to obesity, type 2 diabetes (T2DM), and metabolic syndrome.	More severe metabolic dysfunction with increased risk of cardiovascular and liver-related mortality.
Treatment	Lifestyle modifications (diet, exercise), weight loss, metabolic control (e.g., GLP-1 RAs, SGLT2 inhibitors).	Same as MASLD, but with added focus on anti-inflammatory and antifibrotic strategies (e.g., obeticholic acid, FXR agonists).

Table 2.
Key distinctions between metabolic dysfunction-associated steatosis liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).

species (ROS) for targeted delivery. Examples include pH-sensitive polymers for tumors and dextran-based nanoparticles activated by ROS to enhance immune response [56, 57].

6.3 Peptide-based drug delivery systems

Short amino acid sequences target specific receptors, improving drug localization. EGFR-targeting peptides in liposomes treat lung cancer, and somatostatin-derived peptides target breast and prostate cancers. Recent peptides like RIPL increase selective uptake in cancer cells [17, 58, 59].

6.4 Inorganic nanoparticle-based systems

Dendrimers, mesoporous silica, magnetic, and gold nanoparticles offer high drug loading and targeting. Dendrimers encapsulate DNA and chemo drugs; magnetic nanoparticles are directed by external fields; gold nanoparticles are used in cancer photothermal therapy [18, 60, 61].

7. Targeted nanocarrier strategies to enhance Viscosol efficacy in MASLD

Modern delivery systems can boost Viscosol's bioavailability, liver targeting, and controlled release, enhancing its MASLD therapy potential. Lipid nanoparticles improve solubility and hepatic distribution, reducing side effects [62]. PEG-PLGA polymeric nanoparticles offer sustained release and protect Viscosol from degradation [56]. pH- or ROS-responsive carriers selectively release Viscosol in inflamed liver regions, increasing local drug levels while lowering toxicity [57]. Exosome-based delivery uses natural vesicles for precise liver targeting [63]. Peptide-functionalized nanoparticles bind overexpressed liver receptors, improving targeting and drug accumulation [59]. These strategies maximize Viscosol's therapeutic effect and minimize off-target impacts.

8. Conclusion

MASLD is a progressive metabolic liver disease closely associated with insulin resistance and T2DM. Dysregulated lipid metabolism and chronic inflammation drive its progression. The HFD-STZ diabetic mouse model reliably replicates these human features, making it suitable to test new treatments. Viscosol from *Dodonaea viscosa* effectively inhibited PTP1B, restoring insulin receptor activity and downstream signaling, improving lipid profiles, and enhancing cholesterol transport. It reversed liver fat accumulation, reduced fibrosis markers, and suppressed inflammation. Viscosol's ability to target insulin resistance, lipid disorders, and inflammation makes it a promising multi-target therapy for MASLD and T2DM. These preclinical findings support further clinical research to address the growing burden of metabolic liver disease and diabetes.

Acknowledgements

I express my deepest gratitude to my supervisor, Dr. Imran Ullah Yousafzai, for his guidance and support.

Conflict of interest

The authors declare no conflict of interest.

Author details

Muhammad Asim^{1†}, Aleena Altaf^{1†}, Aamir Sohail¹, Maimoona Arshad¹,
Faiza Noreen¹, Idrees Raza², Hamza Muneer², Muhammad Murtaza Hasnain¹,
Raza Sufyan¹ and Imran Ullah^{1*}

1 Department of Biochemistry, Faculty of Biological Sciences,
Quaid-i-Azam University, Islamabad, Pakistan

2 Department of Biochemistry and Biotechnology, FVAS, Muhammad Nawaz Shareef
University of Agriculture, Multan, Pakistan

*Address all correspondence to: imranullah@qau.edu.pk

† Both authors contributed equally.

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Briseño-Bass P, Chávez-Pérez R, López-Zendejas M. Prevalence of hepatic steatosis and its relation to liver function tests and lipid profile in patients at medical check-up. *Revista De Gastroenterología De México (English Edition)*. 2018;**84**(3):290-295. Available from: <https://www.revistagastroenterologiamexico.org/en-prevalence-hepatic-steatosis-its-relation-articulo-S2255534X18301488>
- [2] Nassir F, Rector RS, Hammoud GM, Ibdah JA. Pathogenesis and prevention of hepatic steatosis. *Gastroenterology and Hepatology (New York)*. 2015;**11**(3):167-175. Available from: <https://pubmed.ncbi.nlm.nih.gov/27099587>
- [3] Fartoux L, Chazouillères O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology*. 2004;**41**(1):82-87. DOI: 10.1002/hep.20519
- [4] Qayyum A, Nystrom M, Noworolski SM, Chu P, Mohanty A, Merriman R. MRI steatosis grading: Development and initial validation of a color mapping system. *American Journal of Roentgenology*. 2012;**198**(3):582-588. DOI: 10.2214/ajr.11.6729
- [5] Lonardo A, Leoni S, Alswat KA, Fouad Y. History of nonalcoholic fatty liver disease. *International Journal of Molecular Sciences*. 2020;**21**(16):5888. DOI: 10.3390/ijms21165888
- [6] Rinella ME, Lazarus JV, Ratzliff V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. 2023;**78**(6):1966-1986. DOI: 10.1097/hep.0000000000000520
- [7] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. Jan 2018;**67**(1):328-357
- [8] Yanai H, Adachi H, Hakoshima M, Iida S, Katsuyama H. Metabolic-dysfunction-associated steatotic liver disease—its pathophysiology, association with atherosclerosis and cardiovascular disease, and treatments. *International Journal of Molecular Sciences [Internet]*. 23 Oct 2023;**24**(20):15473. DOI: 10.3390/ijms242015473
- [9] Yanai H, Hirowatari Y, Ito K, Kurosawa H, Tada N, Yoshida H. Understanding diabetic dyslipidemia by using the anion-exchange high performance liquid chromatography data. *Journal of Clinical Medicine Research*. 2016;**8**(5):424-426. DOI: 10.14740/jocmr2533w
- [10] Leith D, Lin YY, Brennan P. Metabolic dysfunction-associated steatotic liver disease and type 2 diabetes: A deadly synergy. *touchREVIEWS in Endocrinology*. 23 Apr 2024;**20**(2):5. DOI: 10.17925/ee.2024.20.2.2
- [11] Younossi ZM, Henry L. Understanding the burden of nonalcoholic fatty liver disease: Time for action. *Diabetes Spectrum: A Publication of the American Diabetes Association*. 2024;**37**(1):9-19. DOI: 10.2337/dsi23-0010
- [12] Ziolkowska S, Binienda A, Jabłkowski M, Szemraj J, Czarny P. The interplay between insulin resistance, inflammation, oxidative stress,

base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. *International Journal of Molecular Sciences*. 2021;**22**(20):11128. DOI: 10.3390/ijms222011128

[13] Ma Y, Lee G, Heo SY, Roh YS. Oxidative stress is a key modulator in the development of nonalcoholic fatty liver disease. *Antioxidants*. 2021;**11**(1):91. DOI: 10.3390/antiox11010091

[14] Lujan PV, Esmel EV, Meseguer ES. Overview of Non-Alcoholic Fatty liver Disease (NAFLD) and the role of sugary food consumption and other dietary components in its development. *Nutrients*. 2021;**13**(5):1442. DOI: 10.3390/nu13051442

[15] Shan GY, Wan H, Zhang YX, Cheng JY, Qiao DR, Liu YY, et al. Pathogenesis and research progress of nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis. *World Journal of Hepatology*. 2024;**16**(10):1142-1150. DOI: 10.4254/wjh.v16.i10.1142

[16] Sohail A, Murtaza Hasnain M, Ehsan Ul Haq M, Nasir I, Sufyan R, Khan M, et al. Oxidative Stress and Antioxidant Interventions in Type 2 Diabetes [Internet]. *Biochemistry. IntechOpen*; 2024. Available from: DOI: 10.5772/intechopen.1006081

[17] Kołodziej-Sobczak D, Sobczak Ł, Łączkowski KZ. Protein tyrosine phosphatase 1B (PTP1B): A comprehensive review of its role in pathogenesis of human diseases. *International Journal of Molecular Sciences*. 2024;**25**(13):7033. DOI: 10.3390/ijms25137033

[18] Teimouri M, Hosseini H, ArabSadeghabadi Z, Babaei-Khorzoughi R, Gorgani-Firuzjaee S, Meshkani R. The role of protein

tyrosine phosphatase 1B (PTP1B) in the pathogenesis of type 2 diabetes mellitus and its complications. *Journal of Physiology and Biochemistry*. 2022;**78**(2):307-322. DOI: 10.1007/s13105-021-00860-7

[19] Sun Y, Dinunno FA, Tang P, Kontaridis MI. Protein tyrosine phosphatase 1B in metabolic and cardiovascular diseases: From mechanisms to therapeutics. *Frontiers in Cardiovascular Medicine*. 22 Aug 2024;**11**:1445739. DOI: 10.3389/fcvm.2024.1445739

[20] Alanazi AZ, Al-Rejaie SS, Ahmed MM, Alhazzani K, Alhosaini K, Sobaei HMA, et al. Protective role of *Dodonaea viscosa* extract against streptozotocin-induced hepatotoxicity and nephrotoxicity in rats. *Saudi Pharmaceutical Journal*. 2023;**31**(8):101669. DOI: 10.1016/j.jsps.2023.06.002

[21] Uddin Z, Song YH, Ullah M, Li Z, Kim JY, Park KH. Isolation and characterization of protein tyrosine phosphatase 1B (PTP1B) inhibitory polyphenolic compounds from *Dodonaea viscosa* and their kinetic analysis. *Frontiers in Chemistry*. 1 Mar 2018;**6**:40. DOI: 10.3389/fchem.2018.00040

[22] Handy RM, Holloway GP. Insights into the development of insulin resistance: Unraveling the interaction of physical inactivity, lipid metabolism and mitochondrial biology. *Frontiers in Physiology*. 20 Apr 2023;**14**:1151389. DOI: 10.3389/fphys.2023.1151389

[23] Xia JY, Holland WL, Kusminski CM, Sun K, Sharma AX, Pearson MJ, et al. Targeted induction of ceramide degradation leads to improved systemic metabolism and reduced hepatic steatosis. *Cell Metabolism*.

2015;**22**(2):266-278. DOI: 10.1016/j.cmet.2015.06.007

[24] Ferré P, Foufelle F. Hepatic steatosis: A role for *de novo* lipogenesis and the transcription factor SREBP-1c. *Diabetes, Obesity and Metabolism*. 2010;**12**(s2):83-92. DOI: 10.1111/j.1463-1326.2010.01275.x

[25] Iizuka K, Takao K, Yabe D. CHREBP-mediated regulation of lipid metabolism: Involvement of the gut microbiota, liver, and adipose tissue. *Frontiers in Endocrinology*. 3 Dec 2020;**11**:587189. DOI: 10.3389/fendo.2020.587189

[26] Hu Y, Zai H, Jiang W, Ou Z, Yao Y, Zhu Q. The mutual inhibition of FOXO1 and SREBP-1C regulated the progression of hepatoblastoma by regulating fatty acid metabolism. *Mediators of Inflammation*. 2021;**2021**:1-18. DOI: 10.1155/2021/5754592

[27] Arroyave-Ospina JC, Wu Z, Geng Y, Moshage H. Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: Implications for prevention and therapy. *Antioxidants*. 2021;**10**(2):174. DOI: 10.3390/antiox10020174

[28] Todisco S, Santarsiero A, Convertini P, De Stefano G, Gilio M, Iacobazzi V, et al. PPAR alpha as a metabolic modulator of the liver: Role in the pathogenesis of nonalcoholic steatohepatitis (NASH). *Biology*. 2022;**11**(5):792. DOI: 10.3390/biology11050792

[29] Smirne C, Croce E, Di Benedetto D, Cantaluppi V, Comi C, Sainaghi PP, et al. Oxidative stress in non-alcoholic fatty liver disease. *Liver*. 2022;**2**(1):30-76. DOI: 10.3390/livers2010003

[30] Luci C, Bourinet M, Leclère PS, Anty R, Gual P. Chronic inflammation in non-alcoholic steatohepatitis:

Molecular mechanisms and therapeutic strategies. *Frontiers in Endocrinology*. 14 Dec 2020;**11**:597648. DOI: 10.3389/fendo.2020.597648

[31] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nature Medicine*. 2018;**24**(7):908-922. DOI: 10.1038/s41591-018-0104-9

[32] Fernando DH, Forbes JM, Angus PW, Herath CB. Development and progression of non-alcoholic fatty liver disease: The role of advanced glycation end products. *International Journal of Molecular Sciences*. 2019;**20**(20):5037. DOI: 10.3390/ijms20205037

[33] Mucinski JM, Manrique-Acevedo C, Kasumov T, Garrett TJ, Gaballah A, Parks EJ. Relationships between very low-density lipoproteins–ceramides, –diacylglycerols, and –triacylglycerols in insulin-resistant men. *Lipids*. 2020;**55**(4):387-393. DOI: 10.1002/lipd.12244

[34] Amor AJ, Pinyol M, Solà E, Catalan M, Cofán M, Herreras Z, et al. Relationship between noninvasive scores of nonalcoholic fatty liver disease and nuclear magnetic resonance lipoprotein abnormalities: A focus on atherogenic dyslipidemia. *Journal of Clinical Lipidology*. 2017;**11**(2):551-561.e7. DOI: 10.1016/j.jacl.2017.02.001

[35] Heeren J, Scheja L. Metabolic-associated fatty liver disease and lipoprotein metabolism. *Molecular Metabolism*. 2021;**50**:101238. DOI: 10.1016/j.molmet.2021.101238

[36] Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. *Molecular Metabolism*. 2020;**42**:101092. DOI: 10.1016/j.molmet.2020.101092

- [37] Berndsen ZT, Cassidy CK. The structure of apolipoprotein B100 from human low-density lipoprotein. *Nature*. Feb 2025;**638**(8051):836-843. DOI: 10.1038/s41586-024-08467-w
- [38] Khatun I, Zeissig S, Iqbal J, Wang M, Curiel D, Shelness GS, et al. Phospholipid transfer activity of microsomal triglyceride transfer protein produces apolipoprotein B and reduces hepatosteatosis while maintaining low plasma lipids in mice. *Hepatology*. 2011;**55**(5):1356-1368. DOI: 10.1002/hep.25504
- [39] Bian X, Gao W, Wang Y, Yao Z, Xu Q, Guo C, et al. Riboflavin deficiency affects lipid metabolism partly by reducing apolipoprotein B100 synthesis in rats. *The Journal of Nutritional Biochemistry*. 2019;**70**:75-81. DOI: 10.1016/j.jnutbio.2019.04.011
- [40] Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor- α : Role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *Journal of Cellular Biochemistry*. 2017;**119**(1):105-110. DOI: 10.1002/jcb.26174
- [41] Rehman K, Akash MSH, Liaqat A, Kamal S, Qadir MI, Rasul A. Role of interleukin-6 in development of insulin resistance and type 2 diabetes mellitus. *Critical Reviews in Eukaryotic Gene Expression*. 2017;**27**(3):229-236. DOI: 10.1615/critreveukaryotgeneexpr.2017019712
- [42] Kanda H. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *Journal of Clinical Investigation*. 2006;**116**(6):1494-1505. DOI: 10.1172/jci26498
- [43] Feng J, Lu S, Ou B, Liu Q, Dai J, Ji C, et al. The role of JNk signaling pathway in obesity-driven insulin resistance. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2020;**13**:1399-1406. DOI: 10.2147/dmso.s236127
- [44] Hurrle S, Hsu WH. The etiology of oxidative stress in insulin resistance. *Biomedical Journal*. 2017;**40**(5):257-262. DOI: 10.1016/j.bj.2017.06.007
- [45] Ramos-Tovar E, Muriel P. Molecular mechanisms that link oxidative stress, inflammation, and fibrosis in the liver. *Antioxidants*. 2020;**9**(12):1279. DOI: 10.3390/antiox9121279
- [46] Tonks NK. PTP1B: From the sidelines to the front lines! *FEBS Letters*. 2003;**546**(1):140-148. DOI: 10.1016/s0014-5793(03)00603-3
- [47] Delibegovic M, Bence KK, Mody N, Hong EG, Ko HJ, Kim JK, et al. Improved glucose homeostasis in mice with muscle-specific deletion of protein-tyrosine phosphatase 1B. *Molecular and Cellular Biology*. 2007;**27**(21):7727-7734. DOI: 10.1128/mcb.00959-07
- [48] Bettaieb A, Bakke J, Nagata N, Matsuo K, Xi Y, Liu S, et al. Protein tyrosine phosphatase 1B regulates pyruvate kinase M2 tyrosine phosphorylation. *Journal of Biological Chemistry*. 2013;**288**(24):17360-17371. DOI: 10.1074/jbc.m112.441469
- [49] Delibegovic M, Zimmer D, Kauffman C, Rak K, Hong EG, Cho YR, et al. Liver-specific deletion of protein-tyrosine phosphatase 1B (PTP1B) improves metabolic syndrome and attenuates diet-induced endoplasmic reticulum stress. *Diabetes*. 2008;**58**(3):590-599. DOI: 10.2337/db08-0913
- [50] Raza I, Sohail A, Muneer H, Fayyaz H, Uddin Z, Almars AI, et al.

Viscosol treatment ameliorates insulin-mediated regulation of dyslipidemia, hepatic steatosis, and lipid metabolism by targeting PTP1B in Type-2 diabetic mice model. *International Journal of Endocrinology*. 2024;**2024**(1):3914332. DOI: 10.1155/ije/3914332

[51] Sohail A, Fayyaz H, Muneer H, Raza I, Ikram M, Uddin Z, et al. Targeted inhibition of protein tyrosine phosphatase 1b by viscosol ameliorates type 2 diabetes pathophysiology and histology in diabetic mouse model. *BioMed Research International*. 2022;**2022**(1):2323078. DOI: 10.1155/2022/2323078

[52] Bartlett RD, Eleftheriadou D, Evans R, Choi D, Phillips JB. Mechanical properties of the spinal cord and brain: Comparison with clinical-grade biomaterials for tissue engineering and regenerative medicine. *Biomaterials*. 2020;**258**:120303

[53] Cool SK, Geers B, Roels S, Stremersch S, Vanderperren K, Saunders JH, et al. Coupling of drugs containing liposomes to microbubbles improves ultrasound triggered drug delivery in mice. *Journal of Controlled Release*. 2013;**172**(3):885-893

[54] Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Pr  at V. PLGA-based nanoparticles: An overview of biomedical applications. *Journal of Controlled Release*. 2012;**161**(2):505-522

[55] Herdiana Y, Wathoni N, Shamsuddin S, Muchtaridi M. Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges. *OpenNano*. 2022;**7**:100048

[56] Jirapinyo P, Jaroenlapnopparat A, Zucker SD, et al. Combination therapy of endoscopic gastric remodeling with GLP-1RA for the

treatment of MASLD. *Obesity Surgery*. 2024;**34**:1471-1478. DOI: 10.1007/s11695-024-07178-5

[57] Kamerkar S, LeBleu V, Sugimoto H, et al. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature*. 2017;**546**:498-503. DOI: 10.1038/nature22341

[58] Kawaguchi T, Fujishima Y, Wakasugi D, et al. Effects of SGLT2 inhibitors on the onset of esophageal varices and extrahepatic cancer in type 2 diabetic patients with suspected MASLD: A nationwide database study in Japan. *Journal of Gastroenterology*. 2024;**59**:1120-1132. DOI: 10.1007/s00535-024-02158-z

[59] Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, et al. pH-sensitive nano-systems for drug delivery in cancer therapy. *Biotechnology Advances*. 2014;**32**(4):693-710. DOI: 10.1016/j.biotechadv.2013.11.009

[60] Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. *Chemical Society Reviews*. 2013;**42**(3):1147-1235. DOI: 10.1039/c2cs35265f

[61] Perazza F, Leoni L, Colosimo S, Musio A, Bocedi G, D'Avino M, et al. Metformin and the liver: Unlocking the full therapeutic potential. *Metabolites*. 2024;**14**(4):186. DOI: 10.3390/metabo14040186

[62] Vandenberghe L, Wang L, Somanathan S, et al. Heparin binding directs activation of T cells against adeno-associated virus serotype 2 capsid. *Nature Medicine*. 2006;**12**:967-971. DOI: 10.1038/nm1445

[63] Wang J, Mongayt D, Torchilin VP. Polymeric micelles for the delivery of poorly soluble drugs: Preparation and anticancer activity in vitro of paclitaxel incorporated into mixed micelles based on poly (ethylene glycol)-lipid conjugate and positively charged lipids. *Journal of Drug Targeting*. 2005;**13**(1):73-80. DOI: 10.1080/10611860400011935