Current Pharmaceutical Research (CPR)
Vol 1, Issue 3, July-September 2025
Journal Homepage: https://cpr.org.in/

Targeting Metabolic Liver Disorders with Sodium Orthovanadate: A Novel Therapeutic Strategy

[1]Hema Rani, [2]Navdeep Singh, [1]Anjana Devi*

[1] *Department of Pharmacy, School of Pharmaceutical and Health Sciences, Career Point University, Hamirpur (HP)176041.*
[2] *School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh-Punjab 147301.*

Keywords

Non-alcoholic fatty liver disease, Alcoholic fatty liver disease, Sodium orthovanadate, Insulin mimetic, Oxidative stress, Inflammation.

Abstract

Non-alcoholic fatty liver disease and alcoholic fatty liver disease are major hepatic disorders characterized by lipid accumulation, oxidative stress, and inflammation, yet they differ fundamentally in aetiology. While Non-alcoholic fatty liver disease is primarily driven by insulin resistance and metabolic syndrome, alcoholic fatty liver disease arises from chronic alcohol consumption and the hepatotoxic effects of its metabolites. Current therapeutic approaches for both conditions are limited, often relying on lifestyle modifications or nonspecific pharmacological agents. Sodium orthovanadate, an inorganic vanadium compound, has emerged as a novel candidate due to its multifaceted pharmacological profile. Acting as an insulin mimetic, it enhances insulin signalling and glucose uptake, while also exerting potent antioxidant and anti-inflammatory effects. These properties make it uniquely suited to address both metabolic and alcohol-related liver dysfunction. Preclinical studies have demonstrated its ability to reduce hepatic steatosis, normalize lipid profiles, improve mitochondrial function, and suppress inflammatory cytokines. Notably, its mechanism of action in Non-alcoholic fatty liver disease primarily involves modulation of glucose, whereas in alcoholic fatty liver disease, it acts by attenuating oxidative damage and downregulating Necrosis Factor-κB-mediated inflammation. Despite these promising outcomes, clinical translation is constrained by concerns regarding long-term toxicity. Nevertheless, Sodium orthovanadate holds significant potential as a dual-purpose therapeutic agent targeting the complex pathophysiology of fatty liver diseases..

***Corresponding Author:**
Ms. Anjana Devi (anjana.pharmacy@cpuh.edu.in)

Article Info
Received: 22 July 2025, Received in revised form: 19 August 2025, Accepted: 28 August 2025, Available online: 10 October 2025

ISSN: 3049-2955/The authors © 2025, under exclusive license to the Sprout Publication
DOI: https://doi.org/10.63785/2025.1.3. 274283

1. Introduction

Fatty liver disease represents a significant and growing public health burden, encompassing a range of hepatic disorders marked by excessive lipid accumulation in liver cells. Broadly, it is classified into two major forms non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD), both of which share overlapping histological features but differ fundamentally in their etiological origins [1]. The global prevalence of NAFLD has seen a steep rise in recent decades, now affecting nearly 25–30% of the adult population, closely paralleling the surge in metabolic conditions such as obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension. NAFLD is increasingly recognised not only as a hepatic manifestation of metabolic syndrome but also as an independent risk factor for cardiovascular disease [2]. On the other hand, AFLD remains a common consequence of chronic and excessive alcohol consumption, with its incidence particularly high in regions where alcohol intake is culturally ingrained or insufficiently regulate. Though both NAFLD and AFLD result in the deposition of fat in hepatocytes termed hepatic steatosis, they progress along different mechanistic pathways. NAFLD develops in the absence of significant alcohol consumption and is predominantly associated with insulin resistance, altered lipid metabolism, and low-grade chronic inflammation [3]. AFLD, conversely, is driven by the toxic metabolites of ethanol, such as acetaldehyde, and is accompanied by oxidative stress, mitochondrial damage, and an upregulation of inflammatory cytokines [4], [5]. Figure 1 shows progression of liver disease in alcohol-related and non-alcohol-related settings. Despite differences in underlying

pathogenesis, both NAFLD and ALD follow a similar trajectory. Simple steatosis can progress to steatohepatitis either non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH) which may subsequently advance to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC) if left untreated [6].

Current treatment options for fatty liver disease remain limited and largely unsatisfactory. For NAFLD, there is no universally approved pharmacological therapy. Clinical guidelines often emphasise lifestyle interventions, such as dietary modification and increased physical activity, aimed at inducing weight loss and improving insulin sensitivity [7]. While modest weight loss has been shown to improve hepatic histology, long-term adherence is often poor, and sustained benefits remain elusive for many patients. Several drugs, including pioglitazone, vitamin E, and GLP-1 receptor agonists, have demonstrated some efficacy in improving liver enzymes and histological parameters in NASH [8], [9]. However, concerns related to safety, tolerability, and long-term outcomes restrict their widespread use. In the case of AFLD, complete cessation of alcohol intake is the primary therapeutic goal. Supportive measures, including nutritional rehabilitation and the use of corticosteroids in severe alcoholic hepatitis, may offer short-term benefits [10]. Nonetheless, relapse rates are high, and many patients present at advanced stages of disease when therapeutic windows have narrowed significantly. The lack of targeted therapies for AFLD, coupled with the complexity of managing patients with coexisting psychosocial issues, underscores the urgency of developing more effective pharmacological strategies [11], [12].

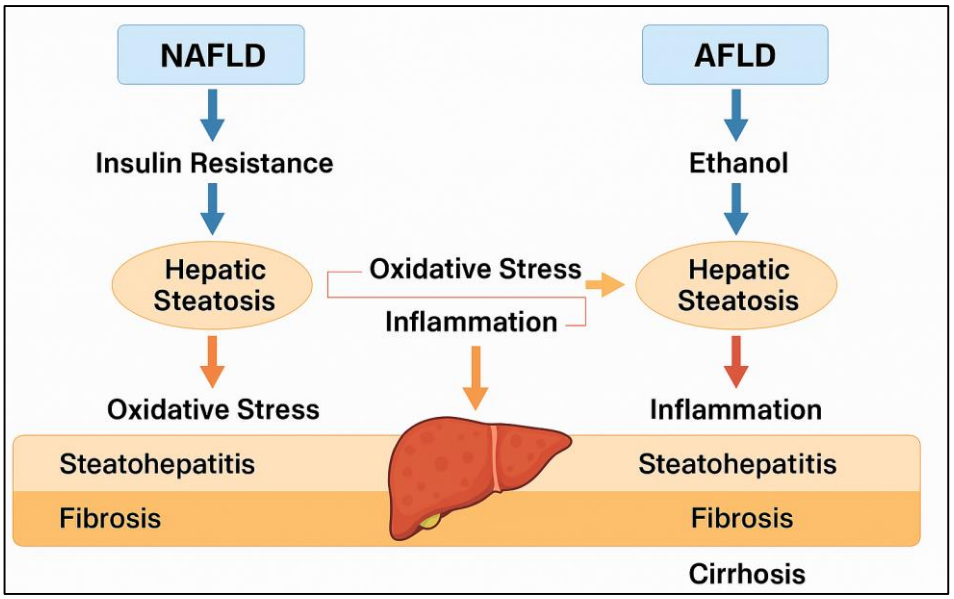

Figure 1: The progression from simple steatosis to more advanced liver pathology.

More recently, the interest has shifted to molecules that can modulate more than one of the pathogenic pathways in fatty liver diseases. An inorganic compound known as sodium orthovanadate, made of vanadium compound, has also become a potential agent because it exerts insulin-mimetic, antioxidant, and anti-inflammatory effects [13]. Vanadium compounds have been investigated and demonstrated to reduce glucose levels in diabetic models, with sodium orthovanadate demonstrating effects of enhancing insulin signalling, decreasing levels of oxidative stress and regulating pro-inflammatory cytokines. Both of these mechanisms can be directly applied to both pathophysiological processes of NAFLD and AFLD, implying a possible therapeutic advantage [14]. Furthermore, the research on experimental models emphasised the possibility of sodium orthovanadate to alleviate liver lipids, enhance mitochondrial activity and protect liver damage against models of metabolic and alcoholic liver disorder. These preclinical results have been promising, though the range of their therapeutic use in the clinical arena is not so fully ploughed [15], [16].

The fact that fatty liver diseases are a multifactorial group and the lack of effective treatment methods mandate the need to explore more on the use of sodium orthovanadate as a two-sided medication. This review attempts to analyse its pharmacological and therapeutic utility for NAFLD and AFLD and provide insight into its mechanism of action, preclinical data, and future potential in hepatology [17], [18].

2. Sodium Orthovanadate: Chemical and Pharmacological Profile

Sodium orthovanadate (Na3VO4) is an inorganic vanadium salt that has attracted some scientific attention because of its wide range of biological activities and potential uses in treatment. It is the sodium salt of orthovanadate acid and is a water-soluble white powder. Pure sodium orthovanadate is soluble in water and forms a series of polymeric and monomeric species of vanadate functions that are altered by the pH, with the orthovanadate ion (VO 4 3 16 19 significantly in alkaline environments [19]. This compound is a vanadium compound with the ion in a

pentavalent state, +5 oxidation state and which is essential to its biochemistry. The presence of phosphate-determined ions mimics the structures of its phosphate ion; therefore, the vanadate ion can interfere with the phosphate-dependent enzyme reactions. This phosphomimetic quality is the basis of most of the biological activity of sodium orthovanadate, especially the regulation of signalling pathways that are involved in cellular metabolism and inflammation [20], [21].

Sodium orthovanadate has a pharmacological action mainly due to its ability to act as inhibitor of a wide panel of phosphatases with particular abilities on protein tyrosine phosphatase (PTPs). Orthovanadate maintains phosphorylation of tyrosine residues in selected intracellular proteins by inhibiting the activity of the phosphotyrosine phosphatase (PTP), therefore, promoting signalling via the receptor tyrosine kinases (RTKs), including the insulin receptor [22]. This leads to the upstream signalling mediated by PI3K/Akt and MAPK pathways that play a central role in controlling the glucose uptake, glycogen production, cell growth as well as survival. Sodium orthovanadate has as such been described as an insulin-mimetic agent, in that it can induce insulin signalling cascades in the absence of endogenous insulin [23], [24]. Such an effect has been demonstrated both in vitro and in vivo, where in both cases administration of orthovanadate has shown to increase the incorporation of glucose in adipose and muscle cells as well as lower the amount of glucose in the blood of a diabetic animal. Beside insulin-mimetic, sodium orthovanadate has antioxidant and anti-inflammatory functions [25]. It has been revealed to minimise production of reactive oxygen species (ROS), avoid activation of nuclear factor-kappa B (NF-κB) and expression of pro-inflammatory cytokine proteins like TNF-α, IL-6, and IL-1β. It is especially applicable to liver diseases because oxidative stress and inflammation are major determinants of the process from simple steatosis to steatohepatitis and fibrosis [26]. Furthermore, orthovanadate is capable of regulating mitochondrial activity and rebalancing the redox state of the cell, further increasing its therapeutic potential in oxidative stress- and metabolic-based conditions [27].

Traditionally, vanadium compounds and sodium orthovanadate have been investigated in numerous experimental contexts. The first of the recognised uses was with diabetes mellitus. Vanadate salts have been proven in animal studies repeatedly to enhance glucose tolerance, abate hyperinsulinaemia and normalise lipids. Despite some positive results of early-stage clinical studies in diabetic patients fears of gastric adverse effects and the overall toxicity of compounds targeted phase III clinical studies and did not proceed [28], [29]. In addition to diabetes, sodium orthovanadate has undergone cancer research since it shows potential to control cell proliferation and apoptosis. It has also shown neuroprotective qualities in animal models of neurodegeneration, assumed to be associated with its antioxidant effects and in its control of intracellular signalling [30]. Recently, focus has been put on how sodium orthovanadate can be used in the case of hepatic and metabolic disorders in relation to cases of insulin resistance and oxidative injury, including NAFLD and AFLD. Orthovanadate in preclinical studies has been able to reduce liver steatosis, enhance liver enzyme status and restore mitochondrial size. Its complex pharmacodynamic effect makes it a compound of interest in conditions where metabolic and pathological phenomena, inflammation, and oxidative stress act at an intersection [31], [32]. Although its actual therapeutic window and safety in the long-term view of liver disease is still to be explained, the evidence on its use shows its possible viability in treating fatty liver disorders, which is why more specialised research and clinical trials should be conducted to picture its usefulness more comprehensively [33].

3. Therapeutic Potential of Sodium Orthovanadate in NAFLD and AFLD

3.1 Metabolic and Hepatic Effects

Sodium orthovanadate is a pentavalent vanadium derivative that has recently gained greater interest in the pharmacological dynamics arena, given its extensive biological activities regarding glucose and lipid metabolism, regulation of oxidative stress, and regulation of inflammatory responses. These properties are especially applicable when dealing with NAFLD and AFLD, which can be characterised by problems with hepatic metabolism and cellular homeostasis [34]. The insulin-mimic and hepatoprotective effects of the compound provide a multidimensional form of therapy, one that targets the metabolic and hepatic disorders that are characteristic of both diseases. By acting at the metabolic level, inhibition of protein tyrosine phosphatases (PTPs), and specifically, PTP1B, a negative insulin receptor signalling regulator, may be regarded as the primary pathway of action of sodium orthovanadate [35], [36]. This suppression maintains insulin receptor phosphorylation and allows the antecedent signal to continue because of the utilisation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, which boosts glucose consumption and metabolism. Therefore, orthovanadate can enhance the sensitivity to insulin and glucose homeostasis, and these are very essential targets in NAFLD [37]. In animal models of diet-induced obesity and insulin resistance, sodium orthovanadate has been shown to produce dramatic reductions in fasting blood glucose and improvements in glucose tolerance, as well as circulating insulin, all of which corrected the metabolic imbalance [38].

Sodium orthovanadate has also shown some positive effects on lipid metabolism in addition to its glucose regulatory effects. Both NAFLD and AFLD are characterised by the presence of hepatic steatosis, whose development entails the lack of equilibrium between intake and elimination of lipids. Orthovanadate was found to inactivate the lipogenic pathway and increasing the oxidation of fatty acids and thereby decreasing the accumulation of triglycerides in liver [39]. In particular, the compound downregulates the expression of the most prominent genes involved in lipogenesis, sterol regulatory element-binding protein-1c (SREBP-1c), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC). At

the same time, it upregulates enzymes related to β-oxidation, including carnitine palmitoyltransferase-1 (CPT-1), to increase clearance of fatty acids within the mitochondria and avoid lipid excess. Sodium orthovanadate plays a role in hepatic cells about stabilisation of the mitochondria and enhanced bioenergetics [40], [41]. By increasing the efficiency of the oxidative phosphorylation process and decreasing the production of reactive oxygen species (ROS), the compound alleviates the dysfunction of mitochondria, one of the main characteristics of NAFLD and AFLD. The result of the enhanced mitochondrial integrity will be the lowered oxidative stress along with the diminished lipid peroxidation, translating into the alleviation of the hepatocellular injury as well as tissue repair [42].

Moreover, sodium orthovanadate offers protection to hepatocytes by regulating the redox status and antioxidant defence mechanisms of a cell. It has also been reported to increase antioxidant capacity including endogenous antioxidants like glutathione (GSH), superoxide dismutase (SOD), and catalase, to combat the oxidative damage caused by accumulation of lipids or during ethanol metabolism. These interventions are especially useful in the AFLD case, as chronic exposure to alcohol causes oxidative stress via the CYP2E1-generated ROS and antioxidant loss in cells [43], [44].

Besides correcting metabolism, sodium orthovanadate modulates inflammatory pathways of signalling, which lead to the development of liver disease. TNF-alpha, IL-6, and IL-1beta: both NAFLD and AFLD experience an up-regulation of so-called inflammatory cytokines, which are essential factors during the development of steatohepatitis out of plain steatosis [45]. Sodium orthovanadate also prevents the activation of NF-kB, which is a main transcription factor that is involved in the expression of inflammatory genes, thus resulting in a decrease in the release of cytokines as well as the mobilisation of immune cells. This anti-inflammatory effect maintains the hepatic architecture and further slows down the fibrogenic process [46], [47]. Further, sodium orthovanadate has revealed hepatoprotective actions under lab conditions, developing ethanol-mediated hepatic damage. It has also been demonstrated to lower the level of ALT, AST, decrease the hepatic necrosis, and normalise histological characteristics of steatosis and inflammation. These enhancements are ascribed not merely to the fact that it neutralises ROS and inflammatory mediators but also to the fact that it stabilises hepatic cell membranes as well as mitochondrial activity [48].

4. Preclinical Studies

A recent experimental investigation and explored the therapeutic effects of SOV in the context of NAFLD using two diet-induced murine models one based on an HFD and the other on a Western diet enriched with sugar-supplemented drinking water (WDS). The study observed that administration of SOV led to notable improvements in metabolic parameters, including significant reductions in body weight, hepatic lipid accumulation, and circulating triglyceride and cholesterol levels [49]. To elucidate the underlying mechanisms, transcriptomic analysis through RNA sequencing was conducted, revealing that the beneficial effects of SOV were associated with enhanced hepatic autophagy, potentially mediated through hypoxia-inducible factor 1 (HIF-1) and autophagy-related gene 5 (ATG5) [50]. The mechanistic role of autophagy was further validated using 3-methyladenine (3-MA), an autophagy inhibitor, in both HepG2 cells and animal models, where its application reversed the protective effects of SOV and restored lipid deposition. These findings suggest that SOV ameliorates NAFLD largely through the activation of autophagic pathways, offering a promising pharmacological approach to managing hepatic steatosis and related metabolic dysfunctions [51], [52].

Yadav and colleagues conducted a study to examine the synergistic effects of SOV and Momordica charantia fruit extract (MFE) on lipid metabolism and enzyme activity in alloxan-induced diabetic rats. Known individually for their antidiabetic potential, both agents were evaluated for their ability to modulate disturbances in lipid profiles and lipogenic enzyme function associated with diabetes [53]. After 21 days of induced hyperglycemia, diabetic rats exhibited marked elevations in serum total lipids, triglycerides, and cholesterol, alongside abnormal lipid accumulation in hepatic and renal tissues. Additionally, alterations in the activities of lipogenic enzymes were noted, reduced in the liver and elevated in the kidney [54]. Treatments with either SOV or MFE alone offered moderate correction of these metabolic imbalances; however, their combination, particularly with a low dose of SOV (0.2%), most effectively normalised the biochemical parameters toward levels observed in non-diabetic controls. This combinatorial approach not only improved lipid homeostasis but also indicated a potentiated hypolipidemic and hypoglycemic action. These findings underscore the therapeutic promise of integrating botanical and trace element-based strategies in the management of diabetes-related dyslipidemia [55], [56].

The long-term metabolic impact of maternal nutrition on offspring by investigating how an HFD during gestation and lactation affects liver function and insulin signalling in mice. The study specifically assessed male offspring of dams exposed to chronic high-fat feeding, analysing both early post-weaning and adult stages. Despite being switched to a normal diet after weaning, these offspring developed hallmark features of metabolic syndrome, including increased visceral fat, elevated serum insulin, TNF-α, and IL-1β levels, suggesting systemic inflammation and insulin resistance [57]. Hepatic analysis revealed significant triglyceride accumulation, heightened activation of stress-related kinases (JNK and IKK), and elevated expression of gluconeogenic enzymes like PEPCK, supporting the development of fatty liver and impaired glucose homeostasis. Notably, insulin signalling and ACC phosphorylation in liver tissue were diminished, indicating compromised metabolic regulation. Similar dysregulation was also observed in

adipose tissue, with reduced phosphorylation of hormone-sensitive lipase [58]. Crucially, these metabolic disturbances were independent of the post-weaning diet, emphasising that early-life exposure to maternal overnutrition can have lasting consequences on hepatic lipid metabolism and insulin sensitivity. This work highlights the transgenerational effect of maternal dietary habits on offspring health and the risk of NAFLD [59], [60].

The effects of SOV and Trigonella foenum-graecum seed powder (TSP) on lipid metabolism in alloxan-induced diabetic rats, focusing on their ability to correct diabetes-associated dyslipidemia and enzyme dysfunction in hepatic and renal tissues. The diabetic condition led to a fourfold increase in blood glucose, along with significant elevations in serum lipids, triglycerides, and cholesterol, and marked lipid accumulation in liver and kidney tissues [61]. Additionally, lipogenic and NADP-linked enzymes such as G6PDH, malic enzyme, and isocitrate dehydrogenase were suppressed in the liver but elevated in the kidney, indicating tissue-specific metabolic disruption. Treatment with SOV and TSP individually improved these parameters, but the combined therapy, especially with a lower dose of SOV (0.2%), was most effective in restoring lipid levels and enzymatic activity close to normal within 21 days. This study highlights the synergistic potential of vanadium-based and plant-derived agents in mitigating lipid abnormalities and enzymatic dysfunction in type 1 diabetes [62], [63].

The synergistic effects of sodium pyrophosphate (PP) and catechin (C) on the oxidative stability and gelling properties of pork myofibrillar protein (MP) under oxidative stress conditions. While both PP and C individually reduced lipid oxidation and protein carbonyl formation, their combination (PP + C) offered the most effective protection. Despite not preventing sulfhydryl and free amine group losses due to oxidation, PP significantly enhanced the solubility, zeta potential, and reduced the mean particle size of MP [64]. It also improved gel breaking strength and cooking yield, leading to better textural quality. In contrast, catechin alone had minimal impact on gelling behavior, aside from slightly reducing the whiteness of the gels. Microscopic analysis revealed that PP-treated MP gels retained a finer and smoother structure resembling non-oxidized controls. Ultimately, the combined use of PP and C resulted in superior oxidative resistance and gel formation, suggesting a promising strategy to enhance the functional quality of muscle proteins in processed meat products [65].

5. Comparative Analysis: NAFLD vs AFLD Response to Sodium Orthovanadate

Sodium orthovanadate, a vanadium-based compound with insulin-mimetic and antioxidant properties, holds potential as a therapeutic agent for both NAFLD and AFLD. Despite sharing common downstream features like hepatic fat accumulation, inflammation, and oxidative stress, NAFLD and AFLD differ fundamentally in their causes. Consequently, the biological response to sodium orthovanadate in these two diseases also varies based on their distinct pathophysiological profiles [66].

In NAFLD insulin resistance is the main determinant usually in combination with obesity, diabetes type II, and metabolic syndrome. Sodium orthovanadate in this case plays its role primarily by imitating insulin-like activity in the body and leading to a normal glucose metabolic process. It potentiates the signal transduction by insulin receptors by restraining the protein tyrosine phosphatases such as PTP1B and facilitating the PI3K/Akt way [67]. This enhances the intake of glucose by the cells and limiting glucose production by the liver which assists in rectifying the metabolic disorder. Moreover, sodium orthovanadate inhibits fat synthesis (lipogenesis) but stimulates fat breakdown (beta- oxidation) in the liver directly reducing fat content in the liver. It also decreases the levels of inflammatory markers and reverses the antioxidant defences, leading to a positive liver histology and a better liver inflammation in experimental models of NAFLD [68].

Alternatively, AFLD develops as a result of habitual alcohol consumption and the resultant liver damage primarily through oxidative stress, accumulation of Acetaldehyde, and immune activation. In that regard, the positive actions of sodium orthovanadate are largely explained by its antioxidant and anti-inflammatory properties instead of imitating insulin. It inhibits the oxidation stress provoked through ethanol, de-activates the ROS production and leaves down the expression of the CYP2E1 enzyme and upregulates the antioxidant enzyme, such as SOD and catalase [69]. Among the immunomodulatory effects of sodium orthovanadate there is the ability to suppress NF-kB signalling and to inhibit the pro-inflammatory cytokines TNF-alpha and IL-6, which may be elevated in AFLD as a result of endotoxin translocation and activation of TLR4 [70].

Although both NAFLD and AFLD benefit from sodium orthovanadate therapy, the therapeutic emphasis differs. In NAFLD, its metabolic modulation is key, while in AFLD, its antioxidant and anti-inflammatory activities are more prominent. Importantly, sodium orthovanadate appears to offer liver-protective effects in both models by targeting shared downstream events like oxidative stress and inflammation. However, clinical application must consider factors like alcohol abstinence in AFLD or long-term toxicity concerns in NAFLD patients requiring chronic treatment [71].

Table 1: Comparative Response of NAFLD vs AFLD to Sodium Orthovanadate.

S. No.	Parameter	NAFLD	AFLD	References

1.	Etiology	Metabolic dysfunction, insulin resistance	Chronic alcohol consumption, acetaldehyde toxicity	[72]
2.	Primary Mechanism of Action	Insulin-mimetic, regulates glucose and lipid metabolism	Antioxidant and anti-inflammatory	[73], [5]
3.	Key Targets	PTP1B inhibition → PI3K/Akt activation	ROS scavenging, CYP2E1 downregulation, NF-κB inhibition	[74]
4.	Lipid Metabolism	↓ Lipogenesis (via SREBP-1c suppression), ↑ β-oxidation	Indirect benefit via reduced oxidative stress	[75], [76]
5.	Inflammation Control	↓ TNF-α, IL-6, MCP-1 (via NF-κB suppression)	↓ Pro-inflammatory cytokines from gut–liver axis activation	[77], [78]
6.	Oxidative Stress Response	↑ Antioxidant enzyme activity (SOD, CAT, GPx)	Potent ROS scavenging and CYP2E1 suppression	[79]
7.	Histological Improvements	Reduced steatosis, improved hepatocyte morphology	Reduced necrosis and inflammatory infiltrates	[80]
8.	Dependence on Lifestyle	Requires long-term correction of metabolic risk factors (diet, exercise, weight loss)	Strict alcohol abstinence is essential	[81], [82]
9.	Potential Limitations	Risk of vanadium accumulation/toxicity with chronic use	Impaired detoxification in alcoholic liver may alter drug handling	[83]

Table 1 summarizes the comparative responses of NAFLD and AFLD to sodium orthovanadate. In NAFLD, which is driven by metabolic dysfunction and insulin resistance, sodium orthovanadate primarily acts as an insulin-mimetic, targeting PTP1B to activate the PI3K/Akt pathway, reduce lipogenesis, enhance β-oxidation, suppress inflammation, and boost antioxidant enzymes. Histologically, it improves steatosis and hepatocyte morphology, though long-term efficacy depends on lifestyle changes and carries potential vanadium toxicity risks [84].

In AFLD, caused by chronic alcohol intake and acetaldehyde toxicity, the compound mainly exerts antioxidant and anti-inflammatory effects, scavenging ROS, downregulating CYP2E1, and inhibiting NF-κB. This leads to reduced oxidative stress, lower pro-inflammatory cytokines, and improved hepatocyte necrosis and inflammation. Its effectiveness relies on strict alcohol abstinence, and impaired detoxification in alcoholic livers may limit drug handling [85].

6. Toxicity and Safety Concerns

Sodium orthovanadate is extensively employed in research laboratories, particularly as a potent phosphatase inhibitor. Despite its utility in scientific studies, it presents significant toxicity concerns that necessitate careful handling and awareness. Acute exposure to sodium orthovanadate can be hazardous through ingestion, inhalation, or dermal contact. Animal studies report an oral LD50 of approximately 330 mg/kg in rats, indicating considerable toxicity when ingested [86]. Similarly, the dermal LD50 stands around 1,100 mg/kg, and inhalation exposure can be lethal at an LC50 of approximately 1.5 mg/L over 4 hours. Classified under the Globally Harmonised System (GHS), sodium orthovanadate carries warnings for acute oral, dermal, and inhalation toxicity, along with skin and eye irritation and potential to cause respiratory discomfort. Prolonged or repeated contact may aggravate irritation to the skin and eyes [87]. At high doses, systemic toxicity may manifest, including convulsions, reproductive complications, and developmental abnormalities in animal studies. Specifically, some reports note reduced maternal weight gain and delayed ossification in fetuses, though no major teratogenic outcomes were observed at doses below 15 mg/kg in mice. Chronic exposure may adversely impact health, although the compound is not currently classified as carcinogenic by international agencies such as the IARC or NTP [88].

To minimise risks, appropriate safety measures should be observed during handling. Personal protective equipment such as gloves, laboratory coats, and eye protection is essential, and work should be conducted in well-ventilated environments to prevent inhalation of harmful dust or vapours. In the event of exposure, immediate first aid should be administered. This includes rinsing the eyes with water, washing affected skin areas with soap and water, moving the exposed individual to fresh air if inhaled, and seeking medical help following ingestion [89]. Environmentally, sodium orthovanadate poses potential risks, particularly to aquatic systems, although comprehensive data on ecological toxicity remain limited. It is recommended to prevent its release into the environment. For storage, the compound should be kept in a tightly sealed container in a cool, dry, and well-ventilated space, away from incompatible substances such as strong oxidisers and acids [90].

7. Future Perspectives

Despite these encouraging results, the long-term use

of sodium orthovanadate is limited by its known toxicity and systemic side effects, particularly with chronic exposure. Addressing these safety concerns will be critical for its successful translation into clinical practice. Future research should focus on developing targeted delivery systems, such as nano formulations or hepatocyte-specific carriers, to maximize therapeutic benefit while minimizing systemic exposure [91]. Additionally, more robust toxicological assessments and well-controlled clinical trials are essential to determine optimal dosing regimens, efficacy endpoints, and patient suitability. Exploring combination therapies with antioxidants, lifestyle interventions, or other hepatoprotective agents may also enhance outcomes and reduce adverse effects. Given the growing global burden of fatty liver diseases and the urgent need for effective treatments, sodium orthovanadate represents a compelling candidate that merits further investigation as part of the next generation of hepatometabolic therapies [92].

Conclusion

Sodium orthovanadate offers a promising and multifactorial approach for the treatment of both NAFLD and AFLD, conditions that currently lack effective and specific pharmacological options. Its ability to simultaneously modulate insulin signalling, improve lipid metabolism, suppress oxidative stress, and inhibit inflammatory pathways positions it as a unique therapeutic agent with dual applicability. In NAFLD, SOV acts predominantly through insulin-mimetic mechanisms by inhibiting protein tyrosine phosphatases and enhancing the PI3K/Akt pathway, thereby restoring glucose homeostasis and reducing hepatic lipogenesis. In AFLD, the therapeutic benefits are largely attributed to its antioxidant capacity, through suppression of ROS generation and mitigation of ethanol-induced inflammatory signalling. Across various animal models, SOV has shown consistent efficacy in reducing hepatic steatosis, improving histological features, and lowering serum markers of liver injury. Furthermore, its synergistic potential with natural agents such as Momordica charantia and Trigonella foenum-graecum opens avenues for combinatorial therapies that may enhance efficacy while minimizing toxicity.

Acknowledgement

The authors gratefully acknowledge the support and facilities provided by the Department of Pharmacy, School of Pharmaceutical and Health Sciences, Career Point University, Hamirpur and School of Pharmacy, Deshbhagat University, Mandi Gobindgarh, Punjab, for the successful completion of this review.

Author Contribution

AD; Conceptualized the study, **HR** and **NS;** prepared the manuscript draft.

Conflict of Interest

No conflicts of interest are disclosed by the authors.

Source of Funding

There is no funding available to conduct this study.

References

1. K. Pafili and M. Roden, “Nonalcoholic fatty liver disease (NAFLD) from pathogenesis to treatment concepts in humans,” 2021. doi: 10.1016/j.molmet.2020.101122.
2. J. T. Haas, S. Francque, and B. Staels, “Pathophysiology and Mechanisms of Nonalcoholic Fatty Liver Disease,” 2016. doi: 10.1146/annurev-physiol-021115-105331.
3. D. Q.-H. Wang, B. A. Neuschwander-Tetri, P. Portincasa, and W. M. Pandak, “Interactions between Bile Acids and Nuclear Receptors and Their Effects on Lipid Metabolism and Liver Diseases,” J. Lipids, 2012, doi: 10.1155/2012/560715.
4. G. Serviddio, “Free Radical biology for medicine: learning from liver disease,” Free Radic. Biol. Med., 2012, doi: 10.1016/j.freeradbiomed.2012.08.076.
5. Shadab Ali, Sayad Ahad Ali, Mukesh Kumar, Iram Jahan, and Jiyaul Hak, “Emerging Strategies for Targeted Drug Delivery across the Blood–Brain Barrier in Neurological Disorder,” Curr. Pharm. Res., pp. 1–14, 2025, doi: 10.63785/cpr.2025.1.1.114.
6. H. E., “Clinical patterns and surveillance strategy for NAFLD-related HCC,” Liver Cancer, 2018.
7. M. D. Beaton, “Current treatment options for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis,” 2012. doi: 10.1155/2012/725468.
8. C. K. Negi, P. Babica, L. Bajard, J. Bienertova-Vasku, and G. Tarantino, “Insights into the molecular targets and emerging pharmacotherapeutic interventions for nonalcoholic fatty liver disease,” 2022. doi: 10.1016/j.metabol.2021.154925.
9. K. Singh et al., “Recent Advances in the Synthesis of Antioxidant Derivatives: Pharmacological Insights for Neurological Disorders,” Curr. Top. Med. Chem., vol. 24, no. 22, pp. 1940–1959, 2024, doi: 10.2174/0115680266305736240725052825.
10. J. Vonderlin, T. Chavakis, M. Sieweke, and F. Tacke, “The Multifaceted Roles of Macrophages in NAFLD Pathogenesis,” 2023. doi: 10.1016/j.jcmgh.2023.03.002.
11. A. Hashem, A. Khalouf, and A. Acosta, “Management of Obesity and Nonalcoholic Fatty Liver Disease: A Literature Review,” 2021. doi: 10.1055/s-0041-1731704.
12. M. R. Khan, D. Kumar, S. Shamim, K. Sunand, S. Sharma, and G. Rawat, “Ethnopharmacological relevance of Citrus limon (L.) Burm. f. as adjuvant therapy,” Ann. Phytomedicine An Int. J., vol. 12, no. 2, pp. 169–179, 2023, doi: 10.54085/ap.2023.12.2.19.
13. M. Yang and C. Y. Zhang, “G protein-coupled receptors as potential targets for nonalcoholic fatty liver disease treatment,” 2021. doi: 10.3748/wjg.v27.i8.677.
14. C. T. Diaconu and C. Guja, “Nonalcoholic Fatty Liver Disease and Its Complex Relation with Type 2 Diabetes Mellitus—From Prevalence to Diagnostic Approach and Treatment Strategies,” 2022. doi: 10.3390/jcm11175144.
15. [15] T. K. Seen et al.,

"Clinical indicators for progression of nonalcoholic steatohepatitis to cirrhosis," 2021. doi: 10.3748/wjg.v27.i23.3238.
16. Shamim, S. Ali, T. Ali, H. Sharma, B. N. Kishor, and S. K. Jha, "Recent Advances in Monodisperse Gold Nanoparticle Delivery, Synthesis, and Emerging Applications in Cancer Therapy," Plasmonics, vol. 20, no. 1, 2025, doi: 10.1007/s11468-024-02732-4.
17. F. M. Sanai, F. Abaalkhail, F. Hasan, M. H. Farooqi, N. Al Nahdi, and Z. M. Younossi, "Management of nonalcoholic fatty liver disease in the Middle East," World J. Gastroenterol., 2020, doi: 10.3748/wjg.v26.i25.3528.
18. Manisha Dev and Pallavi Chandel, "Nanostructured Lipid Carriers in Pulmonary Drug Delivery: Progress and Prospects," Curr. Pharm. Res., pp. 131–143, 2025, doi: 10.63785/cpr.2025.1.1.131143.
19. H. G. Kim, S. G. Jeong, J. H. Kim, and J. Y. Cho, "Phosphatase inhibition by sodium orthovanadate displays anti-inflammatory action by suppressing AKT-IKKβ signaling in RAW264.7 cells," Toxicol. Reports, 2022, doi: 10.1016/j.toxrep.2022.09.012.
20. D. J. White and L. S. Levy, "Vanadium: Environmental hazard or environmental opportunity? A perspective on some key research needs," 2021. doi: 10.1039/d0em00470g.
21. Riya Chandel, Firoz Khan, and Taranvirinderdeep Singh, "The Expanding Role of Sphingolipids in Liver Fibrosis and Disease Progression," Curr. Pharm. Res., pp. 88–104, 2025, doi: 10.63785/cpr.2025.1.2.200214.
22. [22] J. Korbecki et al., "Sodium Orthovanadate Changes Fatty Acid Composition and Increased Expression of Stearoyl-Coenzyme A Desaturase in THP-1 Macrophages," Biol. Trace Elem. Res., 2020, doi: 10.1007/s12011-019-01699-2.
23. [23] J. Korbecki, I. Baranowska-Bosiacka, I. Gutowska, K. Piotrowska, and D. Chlubek, "Cyclooxygenase-1 as the Main Source of Proinflammatory Factors After Sodium Orthovanadate Treatment," Biol. Trace Elem. Res., 2015, doi: 10.1007/s12011-014-0176-4.
24. A. K. Jaiswal et al., "Multi-targeted therapeutic exploration of Tamarix gallica flowers for anti-ulcer activity and associated complications," J. Ayurveda Integr. Med., vol. 15, no. 4, p. 100947, 2024, doi: 10.1016/j.jaim.2024.100947.
25. K. Patel, V. Bora, and B. Patel, "Sodium orthovanadate exhibits anti-angiogenic, antiapoptotic and blood glucose-lowering effect on colon cancer associated with diabetes," Cancer Chemother. Pharmacol., 2024, doi: 10.1007/s00280-023-04596-7.
26. S. Kumar, S. Ivanov, A. Lagunin, and R. K. Goel, "Attenuation of hyperhomocysteinemia induced vascular dementia by sodium orthovanadate perhaps via PTP1B: Pertinent downstream outcomes," Behav. Brain Res., 2019, doi: 10.1016/j.bbr.2019.01.039.
27. P. Kwolek, K. Dychtoń, and M. Pytel, "Orthophosphoric acid solutions of sodium orthovanadate, sodium tungstate, and sodium molybdate as potential corrosion inhibitors of the Al2Cu intermetallic phase," J. Solid State Electrochem., 2019, doi: 10.1007/s10008-019-04397-0.
28. Y. Hasegawa et al., "Neuroprotective effect of postischemic administration of sodium orthovanadate in rats with transient middle cerebral artery occlusion," J. Cereb. Blood Flow Metab., 2003, doi: 10.1097/01.WCB.0000085160.71791.3F.
29. P. Das, D. Kumar, V. Gupta, S. Gupta, R. Tanwar, and K. Behmani, "Sphingosomes: Advancements and Emerging Applications in Advanced Drug Delivery Systems," Curr. Pharm. Res., vol. 1, pp. 199–208, 2025, [Online]. Available: https://cpr.org.in/index.php/files/article/view/134/83
30. A. Morita et al., "Sodium orthovanadate suppresses DNA damage-induced caspase activation and apoptosis by inactivating p53," Cell Death Differ., 2006, doi: 10.1038/sj.cdd.4401768.A. Joshi, A. Akhtar, P. Saroj, A. Kuhad, and S. P. Sah, "Antidepressant-like effect of sodium orthovanadate in a mouse model of chronic unpredictable mild stress," Eur. J. Pharmacol., 2022, doi: 10.1016/j.ejphar.2022.174798.
31. K. Singh et al., "Deciphering the Genetic Landscape: Exploring the Relationship Between HLA-DQA1, HLA-DQB1, and HLA-DRB1 Genes in Diabetes Mellitus," Curr. Pharmacogenomics Person. Med., vol. 21, pp. 1–11, 2024, doi: 10.2174/0118756921310081240821065036.
32. . Kawano et al., "Neuroprotective effect of sodium orthovanadate on delayed neuronal death after transient forebrain ischemia in gerbil hippocampus," J. Cereb. Blood Flow Metab., 2001, doi: 10.1097/00004647-200111000-00003.
33. K. K. Bhopale and M. P. Srinivasan, "Therapeutics for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)," 2023. doi: 10.3390/livers3040040.
34. . Prasoppokakorn, P. Pitisuttithum, and S. Treeprasertsuk, "Pharmacological therapeutics: Current trends for metabolic dysfunction-associated fatty liver disease (mafld)," 2021. doi: 10.14218/JCTH.2021.00189.
35. P. Kumar et al., "7. Fused Deposition Modeling 3D-Printed Scafolds for Bone Tissue.pdf," Appl. Biochem. Biotechnol., vol. 12, no. 22, pp. 1–11, 2024, doi: 10.54085/ap.2023.12.2.19.
36. R. Hegarty, E. Kyrana, E. Fitzpatrick, and A. Dhawan, "Fatty liver disease in children (MAFLD/PeFLD Type 2): unique classification considerations and challenges," 2023. doi: 10.1177/20420188231160388.
37. D. Chua, Z. S. Low, G. X. Cheam, A. S. Ng, and N. S. Tan, "Utility of Human Relevant Preclinical Animal Models in Navigating NAFLD to MAFLD Paradigm," 2022. doi: 10.3390/ijms232314762.
38. S. X. Wang, J. S. Yan, and Y. S. Chan, "Advancements in MAFLD Modeling with Human Cell and Organoid Models," 2022. doi: 10.3390/ijms231911850.

39. D. Garcia-Morena et al., “In Vitro Influence of Specific Bacteroidales Strains on Gut and Liver Health Related to Metabolic Dysfunction-Associated Fatty Liver Disease,” Probiotics Antimicrob. Proteins, 2025, doi: 10.1007/s12602-024-10219-1.
40. B. Pratap, S. Shamim, and S. Ali, “Formulation and Characterisation of Herbal Ethosomal Gel of Luliconazole and Clove Oil for Modified Drug Diffusion to the Skin,” Res. J. Pharm. Technol., vol. 18, no. 8, pp. 3501–3508, 2025, doi: 10.52711/0974-360X.2025.00504.
41. M. Saydmohammed et al., “Quantifying the progression of non-alcoholic fatty liver disease in human biomimetic liver microphysiology systems with fluorescent protein biosensors,” 2021. doi: 10.1177/15353702211009228.
42. T. Shi et al., “Regulation of Mitochondrial Function by Natural Products for the Treatment of Metabolic Associated Fatty Liver Disease,” 2021. doi: 10.1155/2021/5527315.
43. A. Anand et al., “Neuroprotective Efficacy and Complementary Treatment with Medicinal Herbs: A Comprehensive Review of Recent Therapeutic Approaches in Epilepsy Management,” CNS Neurol. Disord. - Drug Targets, vol. 24, no. 1, pp. 60–73, 2024, doi: 10.2174/0118715273332140240724093837.
44. A. Tsuji et al., “Tactics with Prebiotics for the Treatment of Metabolic Dysfunction-Associated Fatty Liver Disease via the Improvement of Mitophagy,” 2023. doi: 10.3390/ijms24065465.
45. S. Khanmohammadi, B. Ramos-Molina, and M. S. Kuchay, “NOD-like receptors in the pathogenesis of metabolic (dysfunction)-associated fatty liver disease: Therapeutic agents targeting NOD-like receptors,” 2023. doi: 10.1016/j.dsx.2023.102788.
46. S. et al. Singh, K., Gupta, J. K., Chanchal, D. K., Khan, S., Varma, A., Shanno, K., Kumar, S., & Shamim, “Deciphering the Genetic Landscape: Exploring the Relationship Between HLA-DQA1, HLA-DQB1, and HLA-DRB1 Genes in Diabetes Mellitus,” Curr. Pharmacogenomics Person. Med., vol. 21, no. 3, pp. 1–11, 2024, doi: 10.2174/0118756921310081240821065036.
47. Á. Rojas, C. Lara-Romero, R. Muñoz-Hernández, S. Gato, J. Ampuero, and M. Romero-Gómez, “Emerging pharmacological treatment options for MAFLD,” 2022. doi: 10.1177/20420188221142452.
48. Y. Li et al., “Preclinical and clinical evidence for the treatment of non-alcoholic fatty liver disease with soybean: A systematic review and meta-analysis,” 2023. doi: 10.3389/fphar.2023.1088614.
49. Y. Oligschlaeger and R. Shiri-Sverdlov, “NAFLD preclinical models: More than a handful, less of a concern?,” 2020. doi: 10.3390/biomedicines8020028.
50. J. M. Eng and J. L. Estall, “Diet-induced models of non-alcoholic fatty liver disease: Food for thought on sugar, fat, and cholesterol,” 2021. doi: 10.3390/cells10071805.
51. S. Chawla, R. Gupta, S. K. Jha, and K. T. Jha, “Stereoisomerism in Chemistry and Drug Development: Optical, Geometrical, and Conformational Isomers,” Med. Chem. (Los. Angeles)., 2025, doi: 10.2174/0115734064366389250923044201.
52. U. C. S. Yadav, K. Moorthy, and N. Z. Baquer, “Combined treatment of sodium orthovanadate and Momordica charantia fruit extract prevents alterations in lipid profile and lipogenic enzymes in alloxan diabetic rats,” Mol. Cell. Biochem., 2005, doi: 10.1007/s11010-005-3703-y.
53. N. P. C. Fernandes, C. V. Lagishetty, V. S. Panda, and S. R. Naik, “An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized Momordica charantia fruit extract,” BMC Complement. Altern. Med., 2007, doi: 10.1186/1472-6882-7-29.
54. H. Sasongko, R. G. Lestari, A. Yugatama, Y. Farida, and Sugiyarto, “Antidiabetic and Antioxidant Effect Combination Vasconcellea pubescens A.DC. And Momordica charantia L. Extract in alloxan-induced diabetic rats,” Pharmacogn. J., 2020, doi: 10.5530/pj.2020.12.49.
55. A. et al. Kumar, J., M., T., Musayev, “Stimuli-responsive Hydrogels for Targeted Antibiotic Delivery in Bone Tissue Engineering,” AAPS PharmSciTech, vol. 26, no. 217, pp. 1–23, 2025, doi: https://doi.org/10.1208/s12249-025-03218-0.
56. S. Saengnipanthkul et al., “Maternal exposure to high-fat diet during pregnancy and lactation predisposes normal weight offspring mice to develop hepatic inflammation and insulin resistance,” Physiol. Rep., 2021, doi: 10.14814/phy2.14811.
57. B. Harmancıoğlu and S. Kabaran, “Maternal high fat diets: impacts on offspring obesity and epigenetic hypothalamic programming,” 2023. doi: 10.3389/fgene.2023.1158089.
58. T. Gali Ramamoorthy et al., “Maternal overnutrition programs epigenetic changes in the regulatory regions of hypothalamic Pomc in the offspring of rats,” Int. J. Obes., 2018, doi: 10.1038/s41366-018-0094-1.
59. P. Kumar et al., “Trends of Nanobiosensors in Modern Agriculture Systems,” Appl. Biochem. Biotechnol., vol. 197, no. 1, pp. 667–690, 2024, doi: 10.1007/s12010-024-05039-6.
60. H. C. Cesar and L. P. Pisani, “Fatty-acid-mediated hypothalamic inflammation and epigenetic programming,” 2017. doi: 10.1016/j.jnutbio.2016.08.008.
61. A. Marco, T. Kisliouk, T. Tabachnik, A. Weller, and N. Meiri, “DNA CpG methylation (5-methylcytosine) and its derivative (5-hydroxymethylcytosine) alter histone posttranslational modifications at the Pomc promoter, affecting the impact of perinatal diet on leanness and obesity of the offspring,” Diabetes, 2016, doi: 10.2337/db15-1608.
62. S. A. Ali, S. Ali, S. Rastogi, B. Shivhare, and M. Muztaba, “A Comprehensive Review on Advancements in Nanocarriers-Based Peptide Delivery for Cancer Therapeutics,” Micro Nanosyst., vol. 17, no. 4, pp. 283–297, 2025, doi: 10.2174/0118764029358553250325040749.

63. M. G. Ross and M. Desai, "The Impact of Maternal Obesity on Offspring Obesity via Programmed Adipogenesis and Appetite," in Parental Obesity: Intergenerational Programming and Consequences, 2016. doi: 10.1007/978-1-4939-6386-7_11.
64. M. Ueno, S. Liu, T. Kiyoi, M. Mogi, and T. Sugiyama, "Long-term impact of maternal dietary intervention on metabolic homeostasis in male offspring in mice," J. Nutr. Biochem., 2022, doi: 10.1016/j.jnutbio.2022.108971.
65. P. Zhang et al., "Similarities and Differences: A Comparative Review of the Molecular Mechanisms and Effectors of NAFLD and AFLD," 2021. doi: 10.3389/fphys.2021.710285.
66. M. Marušić, M. Paić, M. Knobloch, and A. M. Liberati Pršo, "NAFLD, Insulin Resistance, and Diabetes Mellitus Type 2," 2021. doi: 10.1155/2021/6613827.
67. D. M. Tanase et al., "The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD)," 2020. doi: 10.1155/2020/3920196.
68. K. Cusi, "Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: Pathophysiology and clinical implications," 2012. doi: 10.1053/j.gastro.2012.02.003.
69. Z. Zhang, J. Wang, and H. Wang, "Correlation of blood glucose, serum chemerin and insulin resistance with NAFLD in patients with type 2 diabetes mellitus," Exp. Ther. Med., 2018, doi: 10.3892/etm.2018.5753.
70. J. Aron-Wisnewsky et al., "Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders," 2020. doi: 10.1038/s41575-020-0269-9.
71. J. Y. Kim, "Chronic alcohol consumption potentiates the development of diabetes through pancreatic β-cell dysfunction," World J. Biol. Chem., 2015, doi: 10.4331/wjbc.v6.i1.1.
72. M. C. Petersen and G. I. Shulman, "Mechanisms of insulin action and insulin resistance," 2018. doi: 10.1152/physrev.00063.2017.
73. Y. Liu et al., "Inhibition of PI3K/AKT signaling via ROS regulation is involved in rhein-induced apoptosis and enhancement of oxaliplatin sensitivity in pancreatic cancer cells," Int. J. Biol. Sci., 2021, doi: 10.7150/ijbs.49514.
74. O. Villamar-Cruz, M. A. Loza-Mejia, L. E. Arias-Romero, and I. Camacho-Arroyo, "Recent advances in PTP1B signaling in metabolism and cancer," 2021. doi: 10.1042/BSR20211994.
75. Tarmeen Ali, "Nanomedicine Approaches to Overcome Barriers in Pulmonary Drug Delivery for Respiratory Diseases," Curr. Pharm. Res., pp. 30–44, 2025, doi: 10.63785/cpr.2025.1.1.3044.
76. NA, "Textbook Section 15.1 Seven-Transmembrane-Helix Receptors Change Conformation in Response to Ligand Binding and Activate G Proteins," Ncbi.Nlm, 2002.
77. Bhanu Pratap and Pankaj Singh Jadaun, "Hydrogel Microneedles: A Breakthrough in Disease Treatment and Drug Delivery Systems," Curr. Pharm. Res., no. 204101, pp. 60–77, 2025, doi: 10.63785/cpr.2025.1.1.6077.
78. C. Zhang, N. Wang, Y. Xu, H. Y. Tan, S. Li, and Y. Feng, "Molecular mechanisms involved in oxidative stress-associated liver injury induced by chinese herbal medicine: An experimental evidence-based literature review and network pharmacology study," 2018. doi: 10.3390/ijms19092745.
79. T. Karatzas et al., "Histopathological changes and onset of severe hepatic steatosis in rats fed a choline-free diet," Exp. Ther. Med., 2018, doi: 10.3892/etm.2018.6385.
80. H. L. Kim et al., "Lifestyle Modification in the Management of Metabolic Syndrome: Statement from Korean Society of CardioMetabolic Syndrome (KSCMS)," Korean Circ. J., 2022, doi: 10.4070/KCJ.2021.0328.
81. Robin Singh, "Revolutionizing Antimicrobial Therapies Through Biofilm-Targeted Nanomedicine," Curr. Pharm. Res., pp. 78–97, 2025, doi: 10.63785/cpr.2025.1.1.7897.
82. W. X. Ding and L. Yang, "Alcohol and drug-induced liver injury: Metabolism, mechanisms, pathogenesis and potential therapies," 2019. doi: 10.1016/j.livres.2019.11.006.
83. C. Grander, F. Grabherr, A. R. Moschen, and H. Tilg, "Non-Alcoholic Fatty Liver Disease: Cause or Effect of Metabolic Syndrome," 2016. doi: 10.1159/000448940.
84. C. O. Adetunji et al., "Potentialities of nanomaterials for the management and treatment of metabolic syndrome: A new insight," Mater. Today Adv., 2022, doi: 10.1016/j.mtadv.2021.100198.
85. F. Idalsoaga, A. V. Kulkarni, O. Y. Mousa, M. Arrese, and J. P. Arab, "Non-alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease: Two Intertwined Entities," 2020. doi: 10.3389/fmed.2020.00448.
86. C. M. Perdomo, G. Frühbeck, and J. Escalada, "Impact of nutritional changes on nonalcoholic fatty liver disease," Nutrients, 2019, doi: 10.3390/nu11030677.
87. G. Pennisi, C. Celsa, F. Spatola, M. Dallio, A. Federico, and S. Petta, "Pharmacological therapy of non-alcoholic fatty liver disease: What drugs are available now and future perspectives," 2019. doi: 10.3390/ijerph16224334.
88. J. D. Torres-Peña, A. P. Arenas-de Larriva, J. F. Alcala-Diaz, J. Lopez-Miranda, and J. Delgado-Lista, "Different Dietary Approaches, Non-Alcoholic Fatty Liver Disease and Cardiovascular Disease: A Literature Review," 2023.
89. G. Alberti, J. C. Gana, and J. L. Santos, "Fructose, omega 3 fatty acids, and vitamin E: Involvement in pediatric non-alcoholic fatty liver disease," 2020. doi: 10.3390/nu12113531.
90. K. A. McGlynn, J. L. Petrick, and H. B. El-Serag, "Epidemiology of Hepatocellular Carcinoma," 2021. doi: 10.1002/hep.31288.
91. J. Hoozemans, M. De Brauw, M. Nieuwdorp, and V. Gerdes, "Gut microbiome and metabolites in patients with NAFLD and after bariatric surgery: A comprehensive review," Metabolites, 2021, doi: 10.3390/metabo11060353.