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**Name of the Journal: World Journal of Gastroenterology**

**Manuscript NO:**

**Manuscript Type: REVIEW**

**Treatment Options for Alcoholic and Non-Alcoholic Fatty Liver Disease: A Review**

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Treatment options for ALD and NAFLD

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**Author contributions:** All authors equally contributed to this paper with conception, literature review, drafting and critical revision, editing, and approval of the final version.

**Supportive foundation:** This review is the result of work supported with resources and the use of the facilities at the Omaha Veterans Affairs’ Medical Center. Professor Kharbanda is supported by Merit Review grants BX001155 from the Department of Veterans Affairs, Office of Research and Development (Biomedical Laboratory Research and Development.

**Conflict-of-interest statement:** No potential conflicts of interest.

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**Abstract**

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health problems worldwide. These two diseases have similar pathological spectra, ranging from simple hepatic steatosis to liver cirrhosis. Although most people with excessive alcohol or calorie intake experience simple hepatic steatosis, a small percentage develops progressive liver disease. Despite extensive research on understanding the pathophysiology of both these diseases there are still no targeted therapies available. The treatment for ALD remains as it was 50 years ago: abstinence, nutritional support and corticosteroids (or pentoxifylline as an alternative if steroids are contraindicated). As for NAFLD, the treatment modality is mainly directed toward weight loss and comorbidity management. Therefore, new pathophysiology-directed therapies are needed urgently. In this review we delineate the treatment options in ALD and NAFLD, including various new targeted therapies that are currently under investigation.

**Key words:** Alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), Treatment options, Glucocorticoids, Liver transplantation.

**Core tip:** Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health problems worldwide. In this review we delineate the treatment options in ALD and NAFLD, including various new targeted therapies that are currently under investigation.

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**INTRODUCTION**

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health issues whose incidences are on the rise with each passing decade. Alcohol is responsible for approximately 4% of all deaths annually and 5% of all disabilities annually worldwide [1]. The Centres for Disease Control and Prevention [CDC] in 2013 have estimated that in the U.S. acute deaths from alcohol attributable causes have outnumbered deaths from chronic diseases (44,000 to 35,000) ([http://apps.nccd.Cdc.gov/ardi/homepage.aspx](http://apps.nccd.cdc.gov/ardi/homepage.aspx)). Motor vehicle accidents have been considered the leading cause of acute death from alcohol-attributable injuries. While the incidence and prevalence of NAFLD is on the rise with each passing decade, and at present an alarming rate of 25-35% and 5-15% of the general population of Western and Asian countries, respectively, are affected by this disease [2],this proportion is even higher in people with type 2 diabetes (60-70%), obesity and those who are morbidly obese (75-92%) compared to the general population [3-5]. The prevalence of obesity in the United States has increased from 10% to 60% of the total population in the last three decades and is considered to be one of the main factors for the increasing prevalence of NAFLD [6].

The risk factors for both these disease are well known. Patients with ALD consume an excessive amount of alcohol while NAFLD patients are usually obese; have insulin resistance and/or metabolic syndrome. Available data from various studies shows that NAFLD may be the hepatic manifestation of metabolic syndrome [7]. The spectrum of both diseases ranges from benign steatosis to hepatitis to cirrhosis and hepatocellular carcinoma. The majority of patients in both of these diseases have hepatic steatosis which is usually asymptomatic; only 20-35% of these patients progress to steatohepatitis or cirrhosis [8]. Despite an increased understanding of the pathophysiology and risk factors for ALD and NAFLD, we still do not have an appropriate therapeutic regimen for either disease.

The treatment options of ALD have not changed in the last four decades, and abstinence is still the cornerstone of treatment. This is supported by nutrition therapy and steroids [9, 10]. Unfortunately, alcoholic hepatitis which is the most serious manifestation of ALD has a short term mortality of up to 50% in patients that are unresponsive to corticosteroid treatment [11]. Thus, treatment options are limited for patients who are steroid non-responders or have contraindications to steroid usage (upper gastrointestinal bleed, impaired renal functions and sepsis). While the treatment for NAFLD is mainly directed toward attenuating the risk factor such as gradual weight loss by lifestyle modification with a focus on nutrition and exercise [12, 13], other therapies utilizing insulin sensitizers (thiazolidinedione’s) and antioxidants (vitamin E) also have been found to be useful. However, their long term safety and adverse effects is a matter of concern.

Thus, proper therapeutic regimens are needed for these liver diseases. In this review, we present the current therapies as well as upcoming potential new approaches and treatment strategies for both of these diseases.

**ALCOHOLIC LIVER DISEASE TREATMENT:**

**General Management**

For the last 50 years, abstinence has remained the primary therapy for ALD treatment. However, serious symptoms develop with the abrupt cessation of alcohol. Thus, treating the alcohol withdrawal syndrome is extremely important and requires administration of fluid, calories, vitamins and minerals. Unstable patients need to be admitted to a critical care unit and airway protection is often required in patients with hepatic encephalopathy.

**Alcohol withdrawal syndrome**

This syndrome is characterized by symptoms that occur 6-24 hrs after abrupt cessation of alcohol in patients who drink consistently and excessively. Long acting benzodiazepines like chlordiazepoxide or diazepam are administered for prevention of seizures and intermediate acting benzodiazepines like lorazepam are recommended in withdrawal patients who are elderly or have had recent head trauma or liver or respiratory failure [14] . Antiepileptic-like carbamazepine can also be used as a substitute to benzodiazepine for preventing seizures. Antipsychotics like haloperidol can be used if patients have excess agitation or psychotic symptoms [14]. Alcoholics are usually malnourished and deficient in vitamins, especially vitamin B1 (thiamine), thus putting them at risk of developing Wernicke encephalopathy, so all such patients should be given thiamine which needs to be continued for 2-3 months [15]. Thiamine should be given before fluids containing glucose to prevent neurological damage.

**Abstinence**

The first step towards treatment requires the patient to accept the fact that they are dependent and addicted to alcohol. Only after this, can the treatment proceed. Abstinence can resolve alcoholic fatty liver disease and can improve the survival rate of cirrhotic or decompensated liver failure patients. Thus, motivating the patients to abstain from alcohol and follow the proper treatment regime are major steps. However, preventing relapse in such patients has always been a big challenge. Patients can participate in Alcoholics Anonymous groups for self-control and motivation and psychological support by an addiction specialist can also help in maintaining sobriety from alcohol. Recognising and treating any associated psychiatric conditions can be helpful in such patients [16]**.** Pharmacotherapy also helps in maintaining sobriety; drugs like Naltrexone and acamprosate assist in reducing alcohol intake in heavy drinkers [17, 18]. Topiramate has found to be effective in multiple clinical trials in decreasing craving and withdrawal symptoms in alcoholics [19]. Disulfiram, an acetaldehyde dehydrogenase inhibitor, is also being used. It causes accumulation of serum acetaldehyde, which produces unpleasant sensations of nausea, vomiting, abdominal pain and dizziness. Such sensations deter patients from consuming alcohol [20]. Baclofen a gamma-aminobutyric acid-B agonist has also been found effective in promoting abstinence [21].

Smoking and obesity are independent risk factor for the progression of ALD [22, 23]**.** Hence, lifestyle modifications like weight loss and smoking cessation are also helpful.

**Nutritional support**

Most patients with ALD are malnourished, and disease severity often correlates with the degree of malnutrition [24]. Most of the complications of ALD are strongly associated with protein calorie malnutrition [25]. Thus, nutrition support is one of the important steps in ALD treatment. Vitamins (like folate, vitamin B6, vitamin A and thiamine [26]and minerals (like selenium, zinc, copper, and magnesium) are often found to be altered in ALD and some believe that these alterations play a role in initiation and progression of liver injury [27]. Especially, zinc levels are decreased in ALD patients and in animal models, and its supplementation has been shown to improve ALD [28]. A major study has also shown that enteral nutrition reduces infectious complications and improves 1-year mortality in such patients [29, 30].

The American College of Gastroenterology (ACG) and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend 1.2 to 1.5 g/kg/day of protein intake and 35 to 40 kcal/kg/day of body weight for energy intake in patients with ALD [31]. This type of malnourished patient is often predisposed to infections so empiric antibiotic treatment is also advised.

**Glucocorticosteroids**

There have been various clinical trials on the use of corticosteroids for treating ALD patients [32-34]. Despite mixed outcomes, corticosteroids are overall considered beneficial for survival in these patients. Unfortunately, 40% of patients have been found to be unresponsive to corticosteroid, with almost no other treatment options. Hence, new target oriented therapies are critically required for the management of this disease [11].

A meta-analysis which pooled data from 3 randomized control trials, found that patients with modified DF *≥*32 or MELD score ≥ 21 treated with prednisolone at 40 mg/d for 28d and then tapering the dose over 2-4 weeks, conferred a 28-day survival benefit of glucocorticoids (85%) versus placebo (65%), with mortality decreasing from 35% in controls to 15% in patients on steroids [34]**.** Early changes in bilirubin levels (at day 7 of treatment) and the Lille score were used to predict the prognosis following steroid administration [35]. A Lille’s score greater than 0.45 on the 7th day after initiation of the treatment indicated that the patient was unresponsive to steroid therapy and predicted a lower survival rate of 25% at 6 months. Recently this score has been re-classified as complete responders (score ≤ 0.16), partial responders (score 0.16-0.56), and null responders (score ≥ 0.56), and is associated with the 28-d survival rate of 91%, 79% and 53%, respectively, with P < 0.0001) [9]. Steroids have been found to have a significant beneficial eﬀect in complete and partial responders but not in null responders, hence discontinuation of steroid therapy is recommended for non-responders [36]. In addition to non-responders, steroids are generally avoided in patients with gastrointestinal bleeding, chronic hepatitis B virus infection, patients with active infection, and hepatorenal syndrome (HRS) patients because of adverse effects in these patient populations [37].

**Pentoxifylline (PTX)**

Steroids are generally used as the first line of treatment in severe alcoholic hepatitis patients with DF ≥32, except in those with renal failure or HRS or contraindication to steroids [38]. PTX (400 mg 3 times per day for 28 days) is considered to be a substitute in such cases. It decreases pro-inflammatory cytokines like TNF-α which are elevated in ASH and has also been shown to have anti-fibrotic properties [39]. It has also been found to have a mortality benefit by reducing the incidence of HRS [40]. A pilot study in ASH patients using PTX demonstrated reduce mortality and HRS incidence when compared to patients given placebo [41]. These findings were later confirmed in a double blind placebo controlled trial, where PTX had shown a decrease in 28 day mortality compared to placebo (24.5% versus 46%). Also, 50% of those who died in the PTX group developed HRS, while 91.7% who died in the placebo group developed HRS, thus showing that PTX also reduces incidence of HRS in such patients [42]. A study in ASH patients comparing PTX and prednisolone have shown a better survival rate in the PTX group 35.29% *vs* 14.71% in steroids, with reduced mortality mainly thought to be because of a decrease in incidence of HRS and gastro intestinal bleeding in the PTX group, but this study had only a small number of patients [43]. To date, no study has shown an additional survival benefit with PTX and corticosteroid combination treatment [44, 45]. In a recently conducted randomized, multicentered, double-blind trial (STOPAH) which was carried across 65 hospitals in the United Kingdom and recruiting more than a thousand patients, showed no impact of PTX on survival or disease progression in severe NASH patients in comparison to placebo [46, 47]. However, based on a lack of other treatment options, PTX could be used.

**Anti-TNF therapy**

Intestinal gut permeability is increased in chronic alcoholics that promotes the translocation of gut luminal antigens especially endotoxin to reach the liver and enhance TNF-α production [48]. TNF-a has been found to correlate with disease severity in severe alcoholic hepatitis patients [49], and also play a vital role in alcohol induced liver injury in various animal models of alcoholic liver injury [50]. Further, mice deficient in TNF receptor 1 do not develop liver injury when administered alcohol [50]. Based on all of these considerations, various human studies were undertaken using anti-TNF therapy. While initial studies were found to be promising, the results could not be duplicated in larger clinical trials. A large randomized controlled trial comparing prednisolone alone with a combination of prednisolone and infliximab had to be stopped before completion because of an increase in infection rate in the prednisolone and infliximab combination group [51]. Further, patients had to be screened for tuberculosis and nocardia infection prior to participation in the study, thus limiting its clinical utility [52].

**Antioxidants**

Alcohol causes oxidative stress by increasing reactive oxygen species (ROS), and decreasing endogenous antioxidant levels [53]. But to date, all trials examining antioxidants (such as lecithin, β-carotene, vitamin C, vitamin E, allopurinol, desferrioxamine, and N-acetylcysteine) either alone or in combination with steroids have been disappointing [54, 55].

**Liver transplantation**

Liver transplantation remains the definitive therapy for end stage decompensated cirrhosis due to ALD. Severe alcoholic hepatitis patients nonresponsive to steroids have a 3 month mortality rate of 70% and with HRS the mortality rate is ≥ 90% unless the patients get liver transplantation [56, 57]. At present there are very few options for treating severe alcoholic hepatitis patients who are non-responsive to steroids and have a Lille score > 0.56. Thus liver transplantation remains the sole hope for such patients, but the issue of transplantation in alcoholics has always remained controversial. Concerns include the risk of recidivism, poor compliance with postoperative care, and ALD being a self-inflicted disease [58]. Recidivism following transplantation is a major challenge, which occurs at a rate of 10-50% [59, 60]. A meta-analysis reviewing factors responsible for recidivism found 3 major variables: a poor social support system, a family history of alcohol abuse/dependence and pre-transplant abstinence of 6 months or less [61]**.** Thus we need a multidisciplinary approach including Presence of an Alcohol Addiction Unit which can significantly contribute in reducing alcohol relapse after transplantation. Also, there should be a psychological evaluation for any mental illness to determine patient suitability for transplantation.

A majority of transplant programs require the patients to undergo a 6 month period of abstinence prior to transplantation [62]. Studies over the years have provided data both for and against the 6-month abstinence rule. One report suggested that the 6-month period of abstinence would allow the liver to recover with medical treatment and possibly there would be no need for transplantation [63]**.** Another study revealed that some recovery in liver function can take place within 3 months of abstinence while many patients may die during the 6 months of waiting period. This led to the suggestion of possibly reducing the period of abstinence to 3 months [64]. Yet another study has also challenged the 6-month abstinence rule by showing beneficial effects of early liver transplantation in steroid-non-responding severe alcoholic hepatitis patients. In this study patients (with Lille score of 0.88) after 13 days of being unresponsive to steroids were put on the transplant list and it was found that the 6 month survival rate was higher in patients who received early transplantation than those who did not (77% *vs* 23%, *P* < 0.001) [65].

However, patients who have received liver transplantation show a high incidence of de novo cancer [66, 67], lymphoproliferative disorder and skin cancer. In some cases squamous cell carcinoma of the oropharynx or oesophagus has also been detected, likely due to the cumulative eﬀects of smoking and post-transplant immunosuppressive drugs. Also liver transplantation due to ALD is associated with a high rate of cardiovascular complications [68].

**Potential new therapeutic options in Alcoholic Liver Disease :**

Advances in basic science have helped the understanding the pathophysiology of ALD better, thus presenting new treatment options as discussed below.

**Role of probiotics and antibiotics**

Healthy intestinal flora is critically important for our well-being. An alcohol-induced change in the gut microflora plays a major role in the pathogenesis of alcoholic hepatitis. Equally important in liver disease progression is the alcohol-induced increased gut permeability that allows for enhanced translocation of gut luminal antigens, including endotoxin/LPS (component of the cell wall of gram negative bacteria), to reach the liver and promote the synthesis and secretion of various inflammatory cytokines [69].

Various studies have proposed the use of probiotics in restoring the normal bowel flora in patients with ALD [70]. In a study performed on patients with ALD it was shown that using probiotics (Bifidobacterium or Lactobacillus) for 4 weeks enhances and normalizes neutrophil phagocytic capacity and helps in reducing endotoxin driven cytokine levels [71]. A similar study revealed significant improvement in AST, ALT and GGT levels in ALD patients administered probiotics (Bifidobacterium or Lactobacillus) for 5 days [72].Rifaximin, a biochemical derivative of Rifamycin, the drug for hepatic encephalopathy, given for 28 days in a clinical trial decreased systemic endotoxin levels [73]. Indeed blood LPS levels help in predicting response to steroids and mortality of alcoholic hepatitis patients [74]. Thus, modifying the gut microbe flora by probiotics and antibiotics could be a potential therapeutic approach for treating ALD that is being actively pursued.

**Role of S-adenosylmethionine (SAM) and Betaine**

SAM is a key methyl donor that is involved in many methylation reactions critical for liver function. SAM also acts as an antioxidant by activating the pathway for GSH synthesis. Decreased SAM levels have been reported in ALD patients; thus, elevating SAM levels could be a potential therapy. Various animal studies have shown liver injury can be reversed by preventing a decrease in SAM levels [75]. Also SAM administration decreases oxidative stress and hepatic stellate cell activation [76]. A randomized controlled trial using SAM or placebo for 2 years in alcohol cirrhotic patients found that the mortality and liver transplantation rate was higher in the placebo arm than in SAM group (29% versus 12%) [77]. Thus, there is need for long-term, high quality trials in the future to establish its effectiveness.

Along the same line as SAM, betaine treatment has been very effective in improving liver injury in various animal models [78, 79]. By virtue of remethylating homocysteine to generate methionine, betaine not only removes the toxic metabolites homocysteine and S-adenosylhomocysteine, but also generates SAM and normalizes the methylation potential [80]. Betaine is hepato-protective and prevents alcohol-induced steatosis, oxidative stress, apoptosis and abnormal protein accumulation [78, 79], and breakdown of sulphur containing amino acid [81]. Clinical trials using betaine should be conducted.

**Role of targeting various chemokines and interleukins**

Chemokines play a pivotal role in the pathogenesis of alcoholic hepatitis. Studies have shown that various chemokines and their subfamily members, including CXCL5, CXCL6, CXCL10 and CCL20 are notably high in ASH livers compared to normal control livers and higher levels correlate with worse prognosis and outcomes [82, 83]. Of these, CCL20 is the most elevated chemokine in ASH livers that attracts lymphocytes, monocytes, Th17 (Helper T17) cells, and dendritic cells. The consequent production of more chemokines and inflammatory mediators ultimately causes heavy neutrophilic infiltration and liver damage [84, 85]. Additional studies in the future are required to determine if targeting CCL20 and other chemokines can be an effective and safe therapeutic approach in ALD.

IL-8 is one of the most important chemoattractant of neutrophils, which further causes hepatic infiltration as well as increased portal pressure [82]. A higher level of IL-8 in alcoholic hepatitis patients is associated with worse prognosis [82]. A therapeutic approach towards counteracting IL-8 levels should be considered as it will decrease neutrophil infiltration of the liver, and at the same time it will affect the bactericidal activity of neutrophils, which is a matter of concern.

IL-22 plays a critical role in bacterial infections and tissue repair. It is a part of the IL-10 family which decreases the production of various pro-inflammatory cytokines [86]. IL-22 has been found to have anti-apoptotic, antimicrobial, antioxidant and anti-steatotic effects, thus it can be used as a therapeutic option in ALD patients. It has been found that levels of T helper cells producing IL-22 correlate with improvement in alcoholic hepatitis patients [87]. Recombinant IL-22 administration showed improvement of liver injury in ethanol-fed mice [88] and in an animal model of acute hepatitis while blocking the IL-22 receptor led to the worsening of the disease [89]. Thus, upregulating IL-22 levels can be a potential therapy for ALD.

Il-17 increases chemotaxis of neutrophils and various other chemokines and its levels are found to be increased in alcoholic hepatitis [90]. Secukinumab, an anti-IL-17 monoclonal antibody has shown favourable results in clinical trials of rheumatoid arthritis, psoriasis and uveitis [91]. Up until now, no study of this monoclonal antibody has been done in patients with liver disease, which can be a potential therapy.

**Role of endocannabinoids**

Endocannabinoids signalling through cannabinoid receptors, CB-1 and CB-2, has been implicated in the pathogenesis of ALD [92]. Studies using animal models of alcoholic liver injury revealed that CB1-deficient mice are resistant, whereas CB2-deficient mice are more susceptible to fatty liver damage [93, 94]. These findings suggested that therapy targeting CB1 and CB2 receptors should be utilized as an alternative for the management of ALD.

**Role of osteopontin (OPN)**

There is substantial evidence suggesting that OPN plays a notable role in wound healing in response to injury in many organs [95]. It is an extracellular matrix protein with pro-fibrogenic properties, and is found to be highly expressed in alcoholic hepatitis patients [96]. One study demonstrated attenuation of alcohol-mediated liver disease in mice lacking OPN [97]. More studies should be conducted to assess OPN as a potential therapeutic target.

**Stem cell therapy**

Hematopoietic stem cell transplant ion is an evolving field. Though limited research has been performed in this area, in the future it could be a promising therapeutic approach. Recent studies have suggested that stem cell transplantation may reduce liver inflammation and improve fibrosis in patients with liver cirrhosis [98]. Mesenchymal stem cells (MSC) directly inhibit the activation of hepatic stellate cells and may also induce apoptosis of hepatic stellate cells [99]. They have also been reported to stimulate proliferation of endogenous hepatocytes [100, 101]. A pilot study performed on 12 patients with ALD to assess the regenerative capacity of the liver after infusion of bone marrow derived-MSC through the hepatic artery showed improvement in histology according to the Laennec fibrosis system, with an overall decrease in TGF-B, type 1 collagen and smooth muscle actin [102]. In another similar study with 9 cirrhotic patients given bone marrow derived stem cells via the portal vein has shown a significant improvement in the Child-Pugh score and albumin levels [103]**.** Liver function was also reported to be better after stem cell therapy in cirrhotic patients [104]. Results of these studies are encouraging and stem cell therapy could serve as a potential breakthrough treatment for ALD. However, the benefits and safety of stem cells should be examined in a large sized RCT.

**NON-ALCOHOLIC FATTY LIVER DISEASE TREATMENT:**

Similar to ALD there is no effective treatment to date for NAFLD. In the absence of a proven effective therapy, we have to follow a multi-disciplinary approach in NAFLD treatment, where a combination of drugs and factors are taken into consideration to counter multiple pathological risk factors involved in NAFLD. These are discussed below.

**Weight loss, dietary modification and changes in lifestyle**

Treatment is mainly directed towards weight loss and risk factor reduction, as most patients are obese or have metabolic syndrome [105]. A weight loss of 3-5% reduces steatosis while a ≥5-7% drop in weight has been shown to resolve NASH. Greater reductions in weight (i.e., ≥10%) may also improve hepatic fibrosis. Weight loss is mainly due to diet modification and exercise. However, the shortcoming of this approach is the lack of adherence and non-compliance with time [106]. Various studies have shown the benefit of weight loss in NAFLD [107]. Dietary modification also plays a key role since a carbohydrate-rich diet, especially with high fructose, is the major cause of obesity, insulin resistance and NAFLD development [108]. Thus, sugar consumption should be kept at <10% of total caloric intake in a day and a fructose rich diet should be avoided in such patients. Food rich in omega-3 fatty acid should be included and those rich in saturated fat and omega-6 fatty acid should be excluded from the diet [109]. An omega-3 fatty acid rich diet promotes fatty acid oxidation and decreases fatty acid synthesis, thus improving the lipid profile. In various animal models, diet deficient in omega-3 fatty acid has been found to cause NAFLD. Fish and fish oil consumption should be promoted as they are rich in omega-3 fatty acid [110]. Thus, diet and moderate exercise are preferred methods of natural weight loss. A study also exhibited that a combination of diet changes and exercise lowered ALT levels to a greater extent than insulin sensitizers or other hypoglycaemic drugs in NAFLD [111]. Weight loss is also beneficial as it improves the cardiovascular risk profile [112]. Nevertheless, it should be noted that weight loss should be gradual, as very rapid weight loss has been associated with steatohepatitis worsening and also increases risk for liver failure [113] and gallstones [114].

Apart from natural weight loss, drugs like Orlistat and Sibutramine are also being used for controlling weight. Orlistat is a lipase inhibitor, preventing fat absorption in the liver and intestines, thus causing weight loss. Sibutramine on the other hand is a serotonin reuptake antagonist which suppresses appetite. Both have shown to reduce serum transaminase levels and hepatic steatosis [115, 116].

**Insulin sensitizers**

Since NAFLD is closely associated with obesity and metabolic syndrome, and both cause insulin resistance, treatment strategies invariably include agents which sensitize the action of insulin.

**Thiazolidinediones (TZDs)** are peroxisome proliferator activated receptor (PPAR) gamma agonists, which improve hepatic and peripheral insulin sensitivity [117] via increasing plasma adiponectin levels [118]. In addition, adiponectin is also shown to have anti-fibrotic and anti-inflammatory properties. Thus, multiple factors involved in pathogenesis of NAFLD such as high insulin resistance, low adiponectin levels and high pro-inflammatory cytokines are all targeted by these drugs. First generation TZDs (Troglitazone) have shown improvement in steatohepatitis but had to be stopped due to hepatotoxicity [119]. However, it paved the way for second generation TZDs (rosiglitazone and pioglitazone) which are not hepatotoxic and showed improvement in insulin resistance, hepatic steatosis and aminotransferases levels [120, 121]. A long term therapy with second generation TZDs may be required as their benefits tend to reverse on discontinuation; however long term therapy is associated with various adverse effects like congestive heart failure, weight gain, peripheral oedema, anaemia and osteoporosis [122, 123]. Also, it has been found that sole TZD therapy without nutrition and lifestyle changes is often not effective [121]. Thus, we need additional options and studies on a larger population with a combination of other drugs to find safe and efficacious treatment options.

**Metformin** a hypoglycaemic drug is used for treatment of type2 diabetes mellitus. Metformin improves hepatic and peripheral insulin resistance by decreasing hepatic gluconeogenesis, lipogenesis and glucose reabsorption from the gut and increasing fatty acid oxidation [124]. While metformin does not cause weight gain as TZDs, it can cause some minor gastro-intestinal adverse effects and sometimes lactic acidosis is seen in patients with renal impairment. Various studies using metformin in NASH patients have shown improvement in insulin resistance, cholesterol levels and aminotransferase levels but the results are mixed when assessing biopsy-guided improvement in steatosis and NASH activity score (NAS) [125]. Thus, if not as monotherapy, metformin could be a part of a multi- therapeutic regimen in NAFLD patients.

**Lipid-Lowering Agents**

NAFLD is often associated with obesity and metabolic syndrome which is characterized by hypercholesterolemia and hypertriglyceridemia. Therefore, the use of lipid lowering agents could be beneficial. While, clofibrate did not show any beneficial effect on the liver tests or the histological scores [126], gemfibriozil showed improvement in ALT levels in NAFLD patients compared to the placebo [127]. Statins have also been tried but have shown variable and infrequent effects. Nevertheless, lipid-lowering agents should be given to NAFLD patients as most have hyperlipidemia and have high risk of getting cardio-vascular problems.

Ezetimibe, a drug that inhibits the reabsorption of lipids from the intestine and also reduces oxidative stress and serum TNF-α levels [128], reduced hepatic lipid content and ALT levels in a mouse model of NAFLD [129]. Human studies for this drug are awaited.

**UDCA**

This drug has hepatoprotective properties and has been studied in various clinical trials for NAFLD treatment. Initial small studies revealed an improvement in liver enzyme levels and hepatic steatosis [126], but a subsequent RCT showed no improvement in liver histology or aminotransferases [130]. Thus, UDCA is not approved as a monotherapy but is part of a drug combination regime in various trials on NAFLD in progress.

**Vitamin E**

Reactive oxygen species (ROS) are produced by free fatty acid oxidation and thus play an important part in the progression of NASH [131]. Vitamin E and C, decrease oxidative stress and thus have been evaluated in patients with NASH. Vitamin E has been studied in various trials and has shown improvement in liver test and oxidative stress markers but with significantly less improvement in histology[132, 133]. A recent trial using a combination of vitamins E and C for 6 months showed that it is no better than placebo for patients with NASH [134]. One study with a three arm trial involving placebo, UDCA and Vitamin E/UDCA combination showed improvement in histology only in the Vitamin E/UDCA combination arm [135]. Another trial comparing a combination of pioglitazone and vitamin E with vitamin E alone over a period of 6 months showed a decrease in serum ALT in both groups, and significant histologic improvement was only seen in the combination group [136]. A meta-analysis involving high-dose vitamin E supplementation has shown an increase in all-cause mortality and cardio-vascular deaths, thus decreasing the enthusiasm for vitamin E therapy [137]**.**

**PTX**

PTX can be of potential benefit in NAFLD due to its effects on reducing free radical oxidative stress, TNFα levels, and potential anti-fibrotic properties [138]. In some trials, PTX has shown improvement in steatosis, lobular inflammation and ballooning degeneration in comparison to baseline, but improvement was not clinically significant when compared to placebo [139]. In a small RCT with NASH patients comparing PTX with placebo, where PTX given as 400 mg three times per day for a period of 1 year was shown to decrease hepatic steatosis, inflammation and NAS by ≥2 pointsand a modest decrease in fibrosis [140]. This favourable response was due to a reduction in decreasing lipid oxidation, largely free-radical-mediated lipid oxidation [141]. In two recent small RCT evaluating the role of PTX has also shown beneficial effect by improving liver enzymes and histology in NAFLD patients [142, 143]. In a recent meta-analysis it was found that only PTX and OCA improve fibrosis in NASH patients [144]. Therefore, further studies are warranted to determine its role in NAFLD treatment.

**Probiotics**

Similar to alcoholic patients, NAFLD patients also have gut bacterial overgrowth and enhanced gut permeability, which can lead to the paracellular leakage of gut luminal antigens leading to NASH development. Thus, probiotics can be a therapeutic option in NASH patients [145, 146]. In a RCT, NAFLD patients showed improvement in liver enzymes on Lactobacillus bulgaricusandStreptococcus thermophilustreatment compared to placebo [147]. In another study, patients randomized to either a combination of Bifidobacterium longum with fructo-oligosaccharides plus lifestyle modification (diet and exercise) or lifestyle modification alone for 24 weeks [148], showed a significant decrease in steatosis, TNF-alpha, AST and NAS in the combination treatment group. Thus, probiotics could also be a part of a combination therapy in NAFLD patients.

**Angiotensin receptor blockers**

NAFLD is often associated with metabolic syndrome and hypertension is an important component of metabolic syndrome, thus angiotensin receptor blockers can be a part of combination therapy regimen of NAFLD. A small pilot study of patients with NASH treated with losartan showed improvements in necro-inflammation and fibrosis [149]. Larger studies are required to explore their potential in NAFLD.

**Endocannabinoid antagonists**

CB1 and CB2 are two receptors which mediate endocannabinoid (EC) activity. The CB1 receptor is mainly expressed in the brain and liver, while CB2 is mainly expressed in the immune cells. These receptors are found to be upregulated in various liver diseases [150]. Artificial endocannabinoid (anandamide) acting on the CB-1 receptor has been shown to promote diet-induced obesity and hepatic steatosis in mice [151], while CB-1 knockout mice or mice treated with rimonabant (CB-1 receptor antagonist) depicted less steatosis and obesity on a high-fat diet than controls [152]. Thus, altering the activity of the liver EC system could play an important role in preventing progression of fibrosis in NAFLD. Therefore, larger human trials are needed.

**Bariatric surgery**

Steady weight loss with exercise and lifestyle modification has been found to increase insulin sensitivity and improve liver histology in NAFLD but with rapid weight loss via bariatric surgery there is risk of developing hepatic failure especially in cirrhotic patients[153, 154]. Bariatric surgery is mostly done in non-cirrhotic NAFLD patients who are morbidly obese, but it is not recommended as a primary mode of treatment in such patients as there is still a risk of developing liver failure postoperatively.

**Liver Transplantation**

NAFLD patients with end stage decompensated liver disease should be considered for liver transplantation but this is not a permanent cure, as NAFLD has been shown to recur in post-transplant liver [155]. Thus, transplantation does not cure the underlying multifactorial pathway causing NAFLD. Therefore, the goals of therapy before and after transplant should be always towards weight management, proper diet consumption and adequate control of glucose and lipids.

**Potential new therapeutic options in Non-alcoholic Liver Disease:**

With advancement in the field of technology, especially bioinformatics and biogenetics, new therapies are currently being tried in NASH, some of which are reviewed below.

**Caspase inhibition**/ **Emricasan**

Caspases are enzymes which are required for completion of various apoptotic pathways and for stimulation of various cytokines and therefore, can be a potential therapeutic target. Various animal studies in the past have supported this approach [156, 157]**.** Emricasan, a pan-caspase protease inhibitor, has been shown to inhibit apoptosis, inflammation and fibrosis in a preclinical model of NASH. Also in a phase II clinical trial including NAFLD patients it has been shown to significantly decrease serum ALT and cCK18 levels [158]**.** The therapeutic effects of this drug have also been examined in various other liver diseases causing cirrhosis where it has been shown to reduce hepatic venous pressure gradient (HVPG). A phase II trial is ongoing ([NCT02686762](http://gut.bmj.com/lookup/external-ref?link_type=CLINTRIALGOV&access_num=NCT02686762&atom=%2Fgutjnl%2Fearly%2F2016%2F09%2F19%2Fgutjnl-2016-312431.atom)) in NASH patients with fibrosis, to evaluate the efficacy of emricasan (10 mg and 100 mg/day for 72 weeks) with the primary end point of the study being improvement in fibrosis without worsening of NASH and the secondary end point is histological improvement or resolution of NASH (**ClinicalTrials.gov Identifier:** NCT02686762).

**ASK1 inhibitors/ ASK1-I**

Apoptosis-signal-regulating kinase 1/ASK1 (GS-4997) is a kinase which induces apoptosis and fibrosis when activated by stimuli like hyperglycaemia, TGF-β and ROS. This enzyme has been shown to be activated in patients with NASH. ASK1-I given to animal models with established NASH showed a significant reduction in hepatic steatosis, fibrosis, body weight, fasting blood glucose, insulin resistance, lipogenesis, cholesterol biosynthesis, plasma AST/ALT levels, and soluble/insoluble collagen and many metabolic parameters of NASH [159-161]. GS-4997 is currently being investigated in a phase II clinical trial of patients with NASH (ClinicalTrials.gov Identifier: NCT02466516).

**PPAR- alpha & delta agonists (Elafibranor)**

PPAR-alpha is mainly expressed in liver and is principally involved in lipid metabolism, while PPAR-delta is found in various tissues of the body and is involved in fatty acid oxidation and insulin sensitivity. In various animal models, PPAR has been shown to be hepato-protective via its effect on decreasing lipid accumulation, inflammation and fibrosis [162-164].In a RCT [clinicaltrials.gov NCT01694849], a daily dose of 80 or 120 mg Elafibranor vs placebo was given to non-cirrhotic NASH patients for 52 weeks [165]. The primary endpoint of this study (that is resolution of NASH without worsening of fibrosis), was not met. However it was found that patients with an initial NAS of ≥4, with 120 mg/day of drug had significant improvement in hepatic inflammation and its metabolic markers. Thus, the results of this study were described as sub-optimal, and further studies with GFT505 are in phase 3 clinical trials to clarify its efficacy (**ClinicalTrials.gov Identifier:** NCT02704403) (<https://clinicaltrials.gov/ct2/show/NCT02704403>).

**Incretin-based therapies**

Glucagon-like peptide 1 (GLP-1) is an incretin hormone, produced by secreted intestinal mucosa L cells. GLP-1 has a short half-life, as it rapidly degraded by dipeptidyl-peptidase IV (DPP-IV). GLP-1 agonists are resistant to DPP-IV and are useful since they lower blood glucose levels by decreasing glucagon secretion, delaying gastric emptying and stimulating pancreatic β cells to increase insulin secretion. Furthermore, these agonists have a central appetite suppressive effect and weight loss which are favourable for such patients [166]. Certain case reports showed a significant decrease in liver fat in diabetic patients with NAFLD when treated with GLP-1 receptor agonists (exenatide, liraglutide). Also, in obese mouse models it has shown to improve insulin sensitivity and hepatic steatosis [167]. In a clinical trial (LEAN study) with 52 NASH subjects using liraglutide compared to placebo were shown to reach the primary end point (histological resolution of NASH without worsening of fibrosis ) in 39% of patients using liraglutide versus 9% using placebo. The liraglutide treatment group has also shown to improve insulin sensitivity, reduced hepatic glucose production and lipogenesis **(ClinicalTrials.gov-**[**NCT01237119**](http://clinicaltrials.gov/show/NCT01237119)**)** [168, 169]. NAFLD patients have been found to show higher DPP-IV expression, thus an increase in hepatic steatosis [170]. Furthermore, a DPP-IV inhibitor like sitagliptin, decreases hepatic steatosis and serum transaminases levels when given to diabetic NAFLD patients [171, 172]. In a recent randomized, double-blind, placebo controlled study, sitagliptin was shown to be no more effective than placebo for improving hepatic steatosis and fibrosis in NAFLD patients [173]. Thus, GLP-1 agonists and DPP-IV inhibitors can be effective therapeutic agents and require further studies.

**Farnesoid X receptor/FXR agonists (obeticholic acid)**

Obeticholic acid is a farnesoid X receptor agonist. It is a synthetic derivative of natural bile acid chenodeoxycholic acid (CDCA), with potency 100 times more than CDCA. Farnesoid X receptor is a nuclear hormone receptor which regulates bile, cholesterol, glucose and lipid metabolism [174, 175]. These receptors act via multiple pathways and inhibit hepatic lipogenesis, gluconeogenesis, glycogenolysis and also maintain cholesterol balance and improve insulin sensitivity [176, 177]. In various animal models, OCA has shown anti-inflammatory and anti-fibrotic properties and has also improved insulin resistance and hepatic steatosis [178]. In an animal model, OCA was shown to reduce hepatic inflammation and fibrosis and also resulted in decreased intrahepatic vascular resistance and improved portal hypertension [179]. Also in an animal model with advanced cirrhosis, treatment with OCA was shown to reduce gut bacterial translocation which usually occurs due to intestinal barrier disruption from 78.3% to 33.3% (p<0.01). Thus it can be used as an option to prevent bacterial infection in such patients [180]. In a small pilot trial of diabetic patients with NAFLD, it was shown to decrease weight and serum g-glutamyl transferase levels as well as an improvement in liver fibrosis [181]. The multicentre (FLINT trial:NCT01265498) trial, comparing the daily dose of 25 mg OCA with placebo in non-cirrhotic NAFLD patients, has shown a decrease in NAFLD activity score, improvement in hepatic steatosis, and a small decrease in liver fibrosis when compared to placebo [182]. A Phase 3, Double blind RCT Multicenter Study is ongoing right now to evaluate the safety and efficacy of OCA in NASH patients [ClinicalTrials.gov Identifier: NCT02548351]. This trial evaluates the effect of OCA compared to placebo on liver histology in non-cirrhotic NASH patients with stage 2 or 3 fibrosis. 2065 patients are randomized in 1:1:1 to 10 mg, 25 mg OCA group and placebo. An interim analysis is to be done at 18 months and the study is expected to end in 6 years. However, an increase in total cholesterol and triglycerides with a decrease in high density lipoprotein was also seen in the OCA group when compared to placebo [182]. Two phase I studies conducted in healthy individuals given OCA for 14-20 days also reported decreased HDL and increased LDL cholesterol, regardless of dose of OCA (5, 10 or 25 mg daily) [183, 184]. These pro-atherogenic effects can be a concern for NAFLD patients with a high risk for cardiovascular adverse events as they already have dyslipidemia. Therefore, long term larger clinical trials are required to determine its efficacy and safety. Further, combination therapies with FXR agonist and agents that prevent atherosclerosis are warranted. Apart from OCA, various other FXR agonists such as GW4064, PX20606, GS-9674 and INT-767 are being tested. GW4064, PX20606 and GS-9674 are synthetic non-steroidal FXR agonists while INT-767 is a dual agonist on FXR and on TGR5 (the transmembrane G-protein bile acid receptor) and BAR502 is a dual agonist for FXR and GPBAR1 receptors. In various animal models these have been shown to improve histological features, steatosis and fibrosis of NASH [185-188]. Thus clinical trials in humans are awaited for these agents aswell.

**NOX-1/4 inhibitors**

NADPH oxidase (NOX), is an enzyme which catalyses the production of reactive oxygen species (ROS) [189]. In various animal models these enzymes are found to be expressed on hepatic stellate cells and promote liver fibrosis and inflammation [190]. In a murine model, NOX 1/4 inhibitor (GKT137831) has been found to decrease ROS production and fibrotic gene expression, thus decreasing inflammation and fibrosis in the liver [189]. Thus, these agents can have a beneficial effect in decreasing liver fibrosis in NASH patients but require future studies.

**Galectin-3 antagonists**

Galectins are proteins that bind to terminal galactose residues on glycoproteins [191]. They are usually expressed in immune cells and are at very low levels in the body but their levels are increased during inflammation and fibrosis [192, 193]. Galectin-3 knockout mice show lesser hepatic fibrosis after liver injury. GR-MD-02, a galectin-3 inhibitor, has shown a decrease in fibrosis, hepatic steatosis and collagen deposition in various animal models with NASH [194]. phase II clinical trial of GR-MD-02 for the treatment of liver fibrosis in NASH patients is currently underway(ClinicalTrials.gov Identifier: NCT02462967).

**Acetyl CoA carboxylase inhibitor (ACC-I)**

Malonyl CoenzymeA plays a key role in fatty acid metabolism and maintains balance between lipogenesis and lipid oxidation [195]. It promotes fatty acid synthesis, and inhibits β-oxidation of lipids. Malonyl CoA is generated from acetyl CoA and the key enzyme regulating this process is Acetyl CoA carboxylase (ACC). Thus, inhibiting ACC prevents fatty acid synthesis and promotes its oxidation. In a murine model of NAFLD, inhibition of ACC has been shown to decrease hepatic steatosis, lipogenesis and increased insulin sensitivity and fatty acid oxidation [195]. Another animal model with ND-630 (ACC isoezyme 1 and 2 inhibitor) when given chronically to diet-induced obese rats and Zucker diabetic fatty rats was shown to reduce hepatic steatosis, haemoglobin A1c (0.9% reduction) and improved insulin sensitivity[196]. Also in a crossover, randomized, double-blind trial in overweight/ obese subjects, administration of a single dose of NDI-010976 (ACC isoezyme 1 and 2 inhibitor) was shown to inhibit de novo lipogenesis in a dose dependent manner [197]. Together, all these results suggest its usefulness in treating metabolic syndrome, type 2 diabetes mellitus, and fatty liver disease. Thus, large long term clinical trials in humans are needed.

**FGF-21 and FGF-19 analogues:**

FGF-21 (fibroblast growth factor 21) is a hormone which is secreted mainly from the liver. It is a starvation-induced peptide hormone with pleiotropic effects whose levels are mainly increased during fasting [198, 199]. While FGF-21 concentrations are elevated in human subjects with NAFLD, a lack of FGF-21 worsened the metabolic disorders in an animal model of NASH [200]. Conversely, treatment with FGF-21 analogue (BMS-986036) was found to improve insulin sensitivity, hepatic steatosis and decrease lipogenesis [201]. In another animal model of NASH, LY240531 (a FGF-21 variant) was shown to increase fatty acid oxidation by enhancing hepatic mitochondrial oxygen consumption. Also various inflammatory markers and AST and ALT levels were reduced, suggesting an attenuation of liver injury [202]. BMS-986036 is currently being evaluated in a phase II trial of NASH patients **(ClinicalTrials.gov Identifier:** [**NCT02413372**](http://gut.bmj.com/lookup/external-ref?link_type=CLINTRIALGOV&access_num=NCT02413372&atom=%2Fgutjnl%2Fearly%2F2016%2F09%2F19%2Fgutjnl-2016-312431.atom)**).**

FXR activation in terminal ileum by bile acid promotes FGF-19 secretion which, in turn, decreases bile acid synthesis and gluconeogenesis [199]. It also results in activation of the FGFR4 receptor which has a proliferative impact on hepatocytes, thus raising the potential for tumorigenesis [203]. NGM-282, a variant of FGF-19 has been shown to decrease bile acid synthesis and gluconeogenesis without having a tumorigenic effect [199]. In a preliminary pre-clinical study, NGM-282 was shown to improve hepatic steatosis and histological features of NASH in an animal model [204].

**CCR2 and CCR5 inhibitor (cenicriviroc)**

CCR2 and CCR5 are chemokine receptors which are mainly expressed in various immune cells like monocytes, macrophages, Kupffer cells, natural killer cells, T cells and stimulate hepatic stellate cells thus promoting fibrosis. These receptors can be inhibited by cenicriviroc (CVC) which is an inhibitor of the CCR2 and CCR5 receptors. CVC has been shown to decrease fibrosis and inflammation in various animal models of diet-induced NASH or substance-induced NASH [205-208]. There is an ongoing trial (ClinicalTrials.gov Identifier: NCT02217475) with CVC to examine its efficacy in NASH patients with fibrosis. It will compare shorter versus longer CVC treatment and assess correlations between decreased inflammation and fibrosis [209].

**SCD -1 inhibitors (aramchol)**

Aramchol is a synthetic lipid molecule which decreases hepatic fat accumulation by decreasing lipogenesis and increasing fatty acid oxidation by inhibiting stearoyl coenzyme A desaturase 1 (SCD1) enzyme [210]. This drug was found to decrease liver fat content significantly in 60 NAFLD patients who were given 100 or 300 mg of this drug daily for 3 months; the effect of the drug on fibrosis was not determined [210]. A phase II clinical trial of this drug is ongoing on NASH patients with fibrosis (ClinicalTrials.gov Identifier: NCT02279524).

**Lysyl oxidase-like 2 inhibitor( LOXL-2; simtuzumab)**

LOXL-2 is an enzyme which causes cross linkage of collagen, thus preventing it from degradation [211]. This enzyme has been found to promote fibrosis in liver diseases of various etiologies. A monoclonal antibody (simtuzumab) to this enzyme has been studied in various animal models and has shown to decrease fibrosis [212]. Two big trials for this drug are ongoing to examine its efficacy in decreasing fibrosis and preventing progression to cirrhosis in such patients (ClinicalTrials.gov Identifier: NCT01672866). (ClinicalTrials.gov Identifier: NCT01672879).

**Sirtuins (SIRTs)**

SIRTs are information regulator proteins. There are various types of SIRTs found in mammals. SIRT-1, a member of this family of proteins, has shown to have anti-inflammatory effects and increased insulin secretion and sensitivity [213]. A decreased liver expression of SIRT-1 was observed in an animal model of NAFLD [214]. Since SIRT-1 activator (resveratrol) was shown to improve hepatic steatosis and insulin sensitivity [215], SIRT-1 could be a potential target for treatment of NAFLD patients’ in future clinical studies.

**Conclusions**

Both ALD and NAFLD are chronic liver diseases with similar spectrums from simple steatosis to cirrhosis with basic differences only in their etiology. Despite understanding much of the pathophysiology of both diseases, there is still no effective treatment for either disease. ALD treatment basically relies on alcohol abstinence, nutritional support, lifestyle modifications, steroids and symptomatic treatment of complications of cirrhosis for ALD while for NAFL, the main focus of treatment is on weight loss, exercise and the use of insulin sensitizers. Removal of the cause would be the most efficient way of treating both diseases. However, the involvement of several inter-related pathways in the pathogenesis of these diseases indicates that a single therapeutic agent is unlikely to be an effective treatment strategy. Hence, a combination therapy towards multiple targets would eventually be required. Future areas of research also include the safety, efficacy, and ethical considerations of liver transplant in severe ASH for patients who are not responding to medical therapy. Various new target oriented therapies are under investigation for both of these diseases and hopefully soon we will be having an effective multi-therapeutic regimen for each disease.

**Acknowledgments:**

We acknowledge the use of the facilities at the Omaha Veterans Affairs’ Medical Center and a Merit Review BX001155 grant (KKK) support from the Department of Veterans Affairs, Office of Research and Development (Biomedical Laboratory Research and Development).

**Abbreviations:**

Alcoholic liver disease (ALD), Non-alcoholic liver disease (NAFLD), Centres for Disease Control and Prevention (CDC), American College of Gastroenterology (ACG), American Association for the Study of Liver Diseases (AASLD), Tumor necrosis factor alpha (TNF- α), Alcoholic steatohepatitis (ASH), Hepatorenal syndrome (HRS), Pentoxifylline (PTX), [Maddrey's Discriminant Function](https://www.mdcalc.com/maddreys-discriminant-function-alcoholic-hepatitis)  (mDF), Model for End-Stage Liver Disease (MELD), Reactive oxygen species (ROS), [Aspartate](http://www.webmd.com/digestive-disorders/aspartate-aminotransferase-ast) aminotransferase (AST), [Alanine aminotransferase](http://www.webmd.com/digestive-disorders/alanine-aminotransferase-alt) (ALT), [Gamma-glutamyl transferase](http://www.healthline.com/health/gamma-glutamyl-transpeptidase) (GGT), Lipopolysaccharide (LPS), S-adenosylmethionine (SAM), Helper T17 (Th17), Interleukin (IL), Osteopontin (OPN), Mesenchymal stem cells (MSC), Randomized controlled trial (RCT), Peroxisome proliferator activated receptor (PPAR), Thiazolidinedione (TZD), Nonalcoholic steatohepatitis (NASH), NASH activity score (NAS), Ursodeoxycholic acid (UDCA), Apoptosis signal regulating kinase 1 (ASK1), Glucagon like peptide-1 (GLP-1), Dipeptidyl peptidase Ⅳ (DPP Ⅳ), Farnesoid X receptor (FXR), chenodeoxycholic acid (CDCA), Obeticholic acid (OCA), NADPH oxidase (NOX), Cenicriviroc (CVC), Stearoyl coenzyme A desaturase 1 (SCD1), Lysyl oxidase-like 2 inhibitor( LOXL-2), Sirtuins (SIRTs), cenicriviroc (CVC)

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