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| --- | --- | --- | --- | --- |
|  | **Description & mechanism** | **Efficacy in on NAFLD in humans** | **Weight loss in humans** | **References** |
| **ACC inhibitor** | Acetyl-CoA carboxylase (ACC) is a cytosolic enzyme that is the rate limiting step in *de novo* synthesis of fatty acids. Inhibition aims to reduce hepatic lipid by reducing hepatic *de novo* lipogenesis. | Phase 2: reduction of liver fat but increase in plasma triglycerides | No | [(Alkhouri et al., 2020)](https://paperpile.com/c/Q7lYca/qsjA) |
| **ACE inhibitor & Angiotensin Receptor Blockers (ARB)** | Angiotensin-converting enzyme (ACE) 2 is a critical regulator of the renin-angiotensin aldosterone system (RAAS), with the angiotensin receptor being the principal downstream target of the pathway. The RAAS had been implicated in NASH and fibrosis. | Phase 2: insufficient recruitment to determine effect due to many patients already on ACEi or ARBPhase 2: improvement in ALT & fibrosis on valsartan | No | [(McPherson et al., 2017)](https://paperpile.com/c/Q7lYca/SSxV) |
| **Alpha glucosidase inhibitor** | Acarbose is an inhibitor of intestinal alpha-glucosidase, which releases glucose from starch and disaccharides. Its use is associated with improved glycaemic control though generally poorly tolerated due to gastrointestinal side-effects. | Phase 2: improvement in biochemical indices of NAFLD. No histological data. Trial in paediatric NAFLD failed to recruit. | No | [(Hajiaghamohammadi et al., 2013)](https://paperpile.com/c/Q7lYca/QJJ6) https://clinicaltrials.gov/ct2/show/NCT00677521 |
| **Berberine** | Berberine is an organic compound found in many plants that has been traditionally used to treat complications of the metabolic syndrome. | Phase 2: improvement in hepatic fat content on magnetic resonance spectroscopy | No | [(Yan et al., 2015)](https://paperpile.com/c/Q7lYca/0lCh) |
| **Bifidobacterium sp.** | *Bifidobacterium* belongs to the *Bifidobacteria* genera and is a frequently used probiotic either by itself or in combination with other strains. | Trial in progress | No | [(Scorletti et al., 2018)](https://paperpile.com/c/Q7lYca/B5UE) |
| **Biguanide** | Metformin is an antihyperglycaemic agent which improves glucose tolerance and reduces body weight in patients with type 2 diabetes. It decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. | Phase 2: improvement in histological NAS and liver transaminasesPhase 3: no significant improvement in histological features of NAFLD or liver transaminases | Yes | [(Haukeland et al., 2009; Loomba et al., 2009)](https://paperpile.com/c/Q7lYca/dsRg%2BiPW1) |
| **Caspase inhibitor** | Caspases, key mediators of apoptosis, are a family of proteases that cleave their substrates either to cause cell death or to activate cytokines as part of an immune response. Emricasan is an irreversible caspase inhibitor. | Phase 2: no improvement in liver histology in patients with NASH fibrosis on emricasanPhase 2: no improvement in hepatic venous pressure gradient or clinical outcomes in patients with NASH-related cirrhosis and severe portal hypertensionPhase 2: improvement in liver transaminases and biomarkers | No | [(Garcia-Tsao et al., 2020; Harrison et al., 2020; Shiffman et al., 2019)](https://paperpile.com/c/Q7lYca/OzKz%2BTmW9%2BOvtf) |
| **CCR2/CCR5 antagonist** | Cenicriviroc is a dual antagonist of C-C motif chemokine receptor (CCR) types 2 and 5. Blockade has been shown to have anti-inflammatory and antifibrotic properties. | Phase 2: improvement in fibrosis and no significant change in NAS on cenicrivirocPhase 3 in progress | No | [(Friedman et al., 2018)](https://paperpile.com/c/Q7lYca/w5tl)https://clinicaltrials.gov/ct2/show/NCT03028740 |
| **Cholesterol Absorption Inhibitor** | Ezetimibe is a lipid-lowering compound that inhibits intestinal absorption of cholesterol by binding to Niemann–Pick C1-like 1, a cholesterol transporter, and therefore reduces the delivery of cholesterol to the liver. | Phase 2: improvement in biochemical indices of NAFLD on ezetimibe. No histological data. Phase 2: no significant reduction in hepatic fat assessed by MRI proton density fat fraction (PDFF) and liver histology on ezetimibe | No | [(Hajiaghamohammadi et al., 2013; Loomba et al., 2015)](https://paperpile.com/c/Q7lYca/bEHQ%2BQJJ6) |
| **Curcumin** | Curcumin is the active ingredient in turmeric and is widely used as a traditional herbal remedy for a variety of conditions. | Phase 2: improvement in liver fat assessed ultrasonographically and biochemical markers of NAFLDPhase 2: improvement in liver fat assessed ultrasonographically and liver transaminasesFurther trials in progress | No | [(Panahi et al., 2017; Rahmani et al., 2016)](https://paperpile.com/c/Q7lYca/m6nt%2BDHwC) <https://clinicaltrials.gov/ct2/show/NCT04109742>https://clinicaltrials.gov/ct2/show/NCT03864783 |
| **Docosahexaenoic acid** | Docosahexaenoic acid (DHA) is an omega-3 fatty acid which reduces plasma triglycerides. | Phase 2: improvement in liver steatosis assessed ultrasonographically and insulin sensitivity (in children). No change in liver transaminases.Phase 2 trial in progress | No | [(Nobili et al., 2011)](https://paperpile.com/c/Q7lYca/Vyxp) https://clinicaltrials.gov/ct2/show/NCT04198805 |
| **DPP4 inhibitor** | DPP-4 inhibition increases incretin levels through reduced degradation of circulating GLP-1. This results in increased insulin secretion, decreases gastric emptying, and decreases blood glucose levels. | Phase 2: sitagliptin was not significantly better than placebo in reducing hepatic fat or transaminasesPhase 4: improvement in hepatic fat content and liver transaminases on vildagliptin | Yes | [(Cui et al., 2016; Macauley et al., 2015)](https://paperpile.com/c/Q7lYca/yNL1%2B28mR) |
| **Eicosapentaenoic acid** | Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid that reduces hypertriglyceridemia. | Phase 2: no improvement in histological features of NASH or liver transaminases | No | [(Sanyal et al., 2014)](https://paperpile.com/c/Q7lYca/FCZH)  https://pubmed.ncbi.nlm.nih.gov/24818764/ |
| **Fibrates** | Fibrates activate peroxisome proliferator-activated receptor α (PPARα) to alter lipid metabolism and treat primary hypercholesterolemia, mixed dyslipidemia, and severe hypertriglyceridemia.  | Phase 2: no improvement in liver fat assessed by MRI-PDFF on fenofibratePhase 2: improvement in liver trasnaminsases on fenofibratePhase 2: no improvement in intrahepatic triglyceride content on fenofibrate | No | [(El-Haggar and Mostafa, 2015; Fabbrini et al., 2010; Oscarsson et al., 2018; Yaghoubi et al., 2017)](https://paperpile.com/c/Q7lYca/kQ7P%2BecZv%2BwhAt%2B5zpz) |
| **FXR agonist** | FXR agonists promote insulin sensitivity and decrease hepatic gluconeogenesis and circulating triglycerides. Obeticholic acid, a synthetic variant of the natural bile acid chenodeoxycholic acid, is a potent FXR activator.  | Phase 2: improvement in NAS on obeticholic acidPhase 2: reduction in markers of liver inflammation and fibrosis on obeticholic acidPhase 3 trials in progress | No | [(Mudaliar et al., 2013; Neuschwander-Tetri et al., 2015)](https://paperpile.com/c/Q7lYca/RlX0%2B1bX7)<https://clinicaltrials.gov/ct2/show/study/NCT03439254>https://clinicaltrials.gov/ct2/show/NCT02548351 |
| **GLP-1 agonist** | GLP-1 agonists mimic the effects of endogenous GLP-1, thus enhancing glucose-stimulated insulin secretion and lower blood glucose levels.  | Phase 2: improvement of histological steatohepatitis on liraglutide Phase 4: no reduction in hepatic fat on magnetic resonance spectroscopy on liraglutide  | Yes | [(Armstrong et al., 2015; Bizino et al., 2020)](https://paperpile.com/c/Q7lYca/jAo5%2BTklt) |
| **Lactobacillus sp.** | *Lactobacillus* is a genus of Gram‐positive bacteria which convert sugars into lactic acid. It is one of the commonly used probiotics.  | Pilot studies: improvement in liver transaminases on lactobacillus rhamnosusPhase 2 trial in progress  | No | [(Abdel Monem, 2017; Tenorio-Jiménez et al., 2018; Vajro et al., 2011)](https://paperpile.com/c/Q7lYca/YHah%2BlOG0%2Bpyg1) |
| **LXR inhibition** | LXR inhibition reduces the synthesis of fatty acid but expedites lipid oxidation by inhibiting the LXR-a activity and decreasing the expression of SREBP-1c within the liver.  | Phase 2: improvement in hepatic fat content on magnetic resonance spectroscopy on oltiprazPhase 3 trial in progress | No | [(Kim et al., 2017)](https://paperpile.com/c/Q7lYca/Qu9m)https://clinicaltrials.gov/ct2/show/NCT04142749 |
| **N-acetylcysteine** | N-acetylcysteine (NAC) is a glutathione precursor which increases glutathione levels in hepatocytes. Increased glutathione levels limit the production of reactive oxygen species which cause hepatocellular injury.  | Pilot study: No significant change in steatosis assessed ultrasonographically. Improvement in liver transaminasesPhase 2 trial in progress (in children) | No | [(Khoshbaten et al., 2010)](https://paperpile.com/c/Q7lYca/GzUI)https://clinicaltrials.gov/ct2/show/NCT02117700 |
| **Omega-3 polyunsaturated fatty acids (mix)** | n-3 polyunsaturated fatty acids are thought to be able to affect insulin resistance, lipogenesis, and inflammation, which are features of nonalcoholic steatohepatitis.  | Phase 3: PUFA supplementation given, plasma increase in PUFA seen in both treatment and placebo group suggesting off-protocol intake. Plasma increase of PUFAs was correlated with NAS improvement.Phase 2: no improvement in NAS or biochemical markers on PUFA. Improvement in hepatic fat assessed by MRI and computer assisted fat morphometry. Phase 4: no evidence of improvement in liver fat on DHA+EPA. Showed a trend toward a decrease in liver fat percentage with DHA+EPA treatment, but there was strong evidence for contamination with DHA and EPA enrichment in the placebo group and poor adherence to DHA+EPA intervention in the treatment arm. | No | [(Argo et al., 2015; Nogueira et al., 2016; Scorletti et al., 2014)](https://paperpile.com/c/Q7lYca/TvhF%2BzacI%2BtGrc) |
| **PDE inhibitor (Pentoxifylline)** | Pentoxifylline is a methylxanthine derivative that increases red blood cell flexibility, reduces blood viscosity, and decreases platelet aggregation. Therapy with pentoxifylline has been associated with a significant reduction of oxidized fatty acids. | Phase 2: no significant differences in improvement in liver transaminases and histological features of NASH when compared to placeboPhase 2: improvement in overall NAS, steatosis, lobular inflammation and fibrosis assessed histologically. No improvement in hepatocellular ballooning.  | No | [(Van Wagner et al., 2011; Zein et al., 2011)](https://paperpile.com/c/Q7lYca/mQ8m%2BgTiF) |
| **Polyphenol (Resveratrol)** | Resveratrol is a phytoalexin found in many plants including grapes, peanuts and berries. Resveratrol activates SIRT1 and therefore is thought to benefit diseases affected by abnormal metabolic control, inflammation, and cell cycle defects.  | Phase 2: no improvement in hepatic steatosis or biochemical parameters of NAFLDPhase 2: no improvement in hepatic fat content assessed by magnetic resonance spectroscopyPhase 2: no improvement in hepatic fat content assessed by magnetic resonance spectroscopy. Significant increase in liver transaminasesPhase 2: improvement in biochemical parameters and hepatic steatosis grade | No | [(Asghari et al., 2018; Chachay et al., 2014; Faghihzadeh et al., 2014; Kantartzis et al., 2018)](https://paperpile.com/c/Q7lYca/xmEs%2B51V1%2Bjrb3%2BZF39) |
| **PPARalpha-delta agonist** | Elafibranor is a dual PPARalpha-delta agonist which causes a reduction in hepatic expression of pro-inflammatory genes and genes involved in fibrogenesis. | Phase 2: improvement in NASH on elafibranorPhase 2 trial in progressPhase 3 trial in progress | No | [(Ratziu et al., 2016)](https://paperpile.com/c/Q7lYca/bPuh)https://clinicaltrials.gov/ct2/show/NCT03883607https://clinicaltrials.gov/ct2/show/NCT02704403 |
| **Probiotic (mix)** | Probiotics are living, non-pathogenic microorganisms. Many of the probiotics used clinically are part of normal human gut flora. They are used medically and commercially for mainly gastrointestinal illnesses. The exact mechanism of action of probiotics is unknown but hypotheses include preventing growth of pathogenic bacteria and anti-inflammatory effects.  | Phase 2: improvement in fatty liver severity assessed ultrasonographically on VSL#3. No significant change in liver transaminases (in children)Phase 2: improvement in liver transaminases and fatty liver ultrasonographic findings on mixture of lactobacillus and bifidobacterium species (in children)Phase 2: improvement in hepatic triglycerides on magnetic resonance spectroscopy and liver transaminases on mixture of lactobacillus and bifidobacterium speciesPhase 2: improvement in liver transaminases on mixture of lactobacillus and bifidobacterium speciesPilot study: improvement in liver transaminases with L Bulgaricus and S ThermophilusPhase 1&2 trials terminated due to no evidence probiotic would benefit the patient | No | [(Alisi et al., 2014; Aller et al., 2011; Famouri et al., 2017; Nabavi et al., 2014; Wong et al., 2013)](https://paperpile.com/c/Q7lYca/jyjM%2Bf1bU%2BJn3E%2BAdHN%2BPNSw)<https://clinicaltrials.gov/ct2/show/NCT04074889>https://clinicaltrials.gov/ct2/show/NCT03511365 |
| **SCD-1 inhibitor** | SCD1 converts saturated fatty acids to monounsaturated fatty acids. SCD1 deficiency has been demonstrated to prevent liver steatosis in several mouse models of NAFLD. Aramchol is an SCD-1 inhibitor.  | Phase 2: improvement in hepatic fat content on magnetic resonance spectroscopy in a dose-dependent manner on aramcholPhase 3 trial in progress | No | [(Safadi et al., 2014)](https://paperpile.com/c/Q7lYca/TkCs)https://clinicaltrials.gov/ct2/show/NCT04104321 |
| **SGLT2 inhibitor** | SGLT2 inhibitors decrease reabsorption of filtered glucose into the bloodstream via SGLT2 transporter proteins in the kidneys, thus reducing hyperglycaemia. | Phase 4: improvement in hepatic fat content on magnetic resonance spectroscopy on empagliflozinPhase 2: improvement in hepatic fat content assessed by MRI-PDFF on combination therapy of dapagliflozin and omega-3 fatty acids. Dapagliflozin monotherapy did not reduce hepatic fat but reduced hepatocyte injury biomarkersPhase 4: reduction in hepatic fat on MRI-PDFF on dapagliflozin  | Yes | [(Eriksson et al., 2018; Kahl et al., 2020; Latva-Rasku et al., 2019)](https://paperpile.com/c/Q7lYca/3U2U%2BxV8H%2BfI7k) |
| **Silymarin** | Silymarin is a botanical product extracted from milk thistle. It is commonly used as an over the counter supplement in chronic liver diseases. | Phase 2: no improvement in overall NAS. Study limited by substantial number of patients who entered without meeting histological criteriaPhase 2: no significant improvement in overall NAS. Improvement in liver fibrosis | No | [(Navarro et al., 2019; Wah Kheong et al., 2017)](https://paperpile.com/c/Q7lYca/uTM7%2BMySI) |
| **Statin** | Statins are a widely prescribed class of drugs used to lower cholesterol levels. Their mode of action is primarily via inhibition of HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway. They are used routinely in treatment of hyperlipidaemia and cardiovascular disease. | Phase 2: no improvement in hepatic fat assessed by magnetic resonance spectroscopy on pitavastatinPilot study: improvement in NASH histology and biochemical markers on rosuvastatin. No placebo included in this study. Pilot study: no improvement in NASH histology or liver transaminases on simvastatin | No | [(Braun et al., 2018; Kargiotis et al., 2015; Nelson et al., 2009)](https://paperpile.com/c/Q7lYca/L7Ph%2BoxUa%2BvaVx) |
| **Thiazolidinediones** | Thiazolidinediones reduce insulin resistance in adipose tissue, muscle and the liver and were routinely used in the management of type 2 diabetes until restrictions were introduced due to safety concerns. They activate PPAR-gamma receptors, thus altering the transcription of several genes involved in glucose and lipid metabolism. They principally act via expanding adipose storage capacity to reduce insulin resistance. | Phase 3: improvement in hepatic steatosis, lobular inflammation and liver transaminases on pioglitazone. No significant improvement in overall NASH or fibrosisPhase 4: improvement in overall NASH score, fibrosis score and hepatic triglyceride content | No (weight gain) | [(Cusi et al., 2016; Sanyal et al., 2010)](https://paperpile.com/c/Q7lYca/tHJK%2BKOnO) |
| **UDCA and Tauroursodeoxycholic acid (TUDCA)** | Ursodeoxycholic acid (UDCA) is a natural secondary bile acid. It slows the rate of intestinal cholesterol absorption and facilitates bile flow. It is used in gallstone disease and primary biliary cirrhosis.TUDCA is a bile acid taurine conjugate derived from ursodeoxycholic acid (UDCA). It is used widely as an over the counter supplement however, unlike UDCA, it is not licenced for medical purposes. | Phase 2: no improvement in overall NAS or biochemical parameters. Improvement in lobular inflammation as a single histological variablePhase 2: improvement in liver transaminases, metabolic parameters and serum markers of fibrosisRCT: no improvement in histological or biochemical parameters compared to placebo | No | [(Leuschner et al., 2010; Lindor et al., 2004; Ratziu et al., 2011)](https://paperpile.com/c/Q7lYca/wWB6%2BgprD%2BeCd6) |
| **Vitamin D** | Vitamin D is a key regulator in the parathyroid hormone axis and thus in calcium and phosphate homeostasis. The role of vitamin D has been extended to a wide range of disease processes including metabolic conditions. Deficiency is common in patients with NAFLD. | Phase 2: improvement in liver transaminasesPhase 2: no improvement in biochemical parametersPhase 2: no improvement in hepatic fat fraction assessed by magnetic resonance or in biochemical parameters  | No | [(Barchetta et al., 2016; Dabbaghmanesh et al., 2018; Geier et al., 2018)](https://paperpile.com/c/Q7lYca/imt8%2BRRes%2BgnO1) |
| **Vitamin E** | Vitamin E is an antioxidant which acts as a free radical scavenger, and is widely used as a vitamin supplement. Oxidative stress has been implicated in NAFLD progression and is a target of treatment approaches.  | Phase 3: improvement in overall NAS and hepatocellular ballooning. No significant improvement in individual histological scores for steatosis, inflammation, fibrosis or in biochemical parametersPhase 2: no significant difference in biochemical parameters of NAFLD between lifestyle interventions + placebo and lifestyle interventions + vitamin E (in children)Phase 2 trial in progress | No | [(Nobili et al., 2006; Sanyal et al., 2010)](https://paperpile.com/c/Q7lYca/tHJK%2BPlmw)https://clinicaltrials.gov/ct2/show/NCT04198805 |

**Supplementary File 1. Narrative summary of evidence in humans for drug classes included in this meta-analysis.**

Descriptions of the principle liver-related findings from randomised controlled trials (RCT) both adults and children with NAFLD with references to completed, published studies or protocols for ongoing trials. A dichotomous assessment of whether the drug is associated with weight loss in humans has been added. ACC, Acetyl-CoA carboxylase; ACE, angiotensin-2 converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; CCR, chemokine receptor; DHA, Docosahexaenoic acid; DPP4, Dipeptidyl-peptidase 4; EPA, eicosapentaenoic acid; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; LXR, Liver X receptor; MRI, magnetic resonance imaging; NAC, N-acetylcysteine; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; PDE, Phosphodiesterase; PDFF, proton-density fat fraction; PPAR, Peroxisome proliferator-activated receptor; PUFA; omega-3 polyunsaturated fatty acid; RAAS, renin-angiotensin-aldosterone system; SCD1, Stearoyl–CoA desaturase-1; SGLT2, Sodium-glucose co-transporter-2; TUDCA, Tauroursodeoxycholic acid; and UDCA, Ursodeoxycholic acid.

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