

# Pharmacologic Therapy with Niacin for Nonalcoholic Fatty Liver Disease (NAFLD): Emerging Evidence

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## Abstract

New evidence indicates that niacin (not as a vitamin, but at pharmacologic doses) may treat nonalcoholic fatty liver disease. *In vivo* and *in vitro* data demonstrate that niacin reverses hepatic steatosis, inflammation (steatohepatitis), and prevents fibrosis. Steatosis significantly decreased 47% from baseline in a small clinical trial associated with reductions in liver enzymes and inflammatory marker C-Reactive Protein. Mechanism is oxidative stress reduction, diacylglycerol acyltransferase-2 (DGAT-2) inhibition. Niacin offers the opportunity for combination therapy with other drugs in development for enhanced synergistic efficacy. Advantages include immediate availability for clinical trials, treats atherogenic dyslipidemia and atherosclerotic cardiovascular disease (ASCVD) commonly seen in NAFLD patients. Randomized clinical trials are urgently needed for a potential cost-saving treatment for this serious disease with no approved treatment at present.

**Keywords:** Niacin, Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis, Fibrosis, Oxidative Stress, Diacylglycerol acyltransferase-2, Niacin Extended-Release

**Abbreviations:** ACC: Acetyl-Coenzyme A Carboxylase; ASCVD: Atherosclerotic Cardiovascular Disease; CRP: C-Reactive Protein; DGAT2: Diacylglycerol Acyltransferase-2; DNL: *De Novo* Lipogenesis; GPR109A: G-Protein Receptor 109A; GPx: Glutathione Peroxidase; GSH: Glutathione, Reduced; HCAR2: Hydroxycarboxylic Acid Receptor-2; H<sub>2</sub>O<sub>2</sub>: Hydrogen Peroxide; HepG2: Hepatoblastoma Cell Line; MPO: Myeloperoxidase; NAFLD: Non-alcoholic Fatty Liver Disease; NASH: Non-alcoholic Steatohepatitis; Niacin ER: Niacin Extended-Release; ROS: Reactive Oxygen Species; TG: Triglycerides; TGF- $\beta$ : Transforming Growth Factor- $\beta$ ; VLDL: Very Low Density Lipoprotein

## Introduction

In pharmacologic doses niacin (nicotinic acid) has been used clinically for over six decades for atherogenic dyslipidemia and reduction of cardiovascular event risk [1]. In combination with statin therapy, it effects regression of coronary atherosclerosis [2,3]. Emerging evidence indicates a new potential use for niacin for the treatment of NAFLD and its complications [4]. Despite this enormous amount of data on niacin, there is confusion and misconceptions about its use of a drug rather than as a vitamin, its formulations, and how it can be used in clinical practice. The purpose of this invited brief communication is to update and summarize this emerging evidence. We

comment on how it may be valuable in the context of other drugs-in-development for NAFLD, especially for combination therapy for synergistic efficacy.

Results of recent phase 2 and 3 clinical trials of several drugs for NAFLD/NASH have been very disappointing [5]. These very costly trials failed to either reach primary endpoints or revealed limited efficacy and tolerability. Most discouraging are 4 recent phase 3 trials in which 2 failed completely (Elafibanor and Selonsertib, [6,7] and two drugs (Cenicriviroc and Obeticholic Acid) showed at least 1 stage reduction in fibrosis but no resolution of NASH [8,9]. Obeticholic Acid raised LDL-Cholesterol and caused itching as a nuisance side effect. However, as of this

writing, the FDA has not yet approved any drug for clinical use for NASH/NAFLD. Other drugs have been suspended from further development including seladelpar, emricasan, selonsertib.

The road to a successful drug is a very steep challenge. NAFLD is a slow liver disease that takes decades to progress from steatosis, steatohepatitis, fibrosis and finally manifesting clinically as cirrhosis. The ultimate test of a drug for success for NAFLD is “clinical benefit” by demonstrating significant reduction in life threatening decompensated cirrhosis complications including liver failure, variceal hemorrhage, encephalopathy, liver cancer, or death. However, to encourage drug development, regulatory authorities (e.g. FDA in the USA) have allowed the use of surrogate endpoints such as biopsy proven reduction in fibrosis score or resolution of NASH for initial approval for clinical use and contingent upon successful clinical benefit. No drug or drug combinations are anywhere near showing clinical benefit. The recent clinical trial failures have set the clock backwards in the search for a remedy for this disease that is of public health concern worldwide.

It is well known that most patients with NAFLD die of cardiovascular disease [10,11]. It is noteworthy that NAFLD and atherosclerosis are often found in the same patient. This is not surprising as these two diseases are characterized by fat deposition, lipotoxicity, inflammation and fibrosis. Thus, drugs for NAFLD/NASH should not increase ASCVD risk by increasing LDL-cholesterol (FXR agonists) or triglycerides (e.g. ACC Inhibitors). The optimal drug would be one that hits the front end of the disease (steatosis) and inflammation (NASH) and the rear end of fibrosis and mitigates ASCVD risk. Such a drug or a combination of drugs would be expected to decrease cirrhosis directly and indirectly as well as atherosclerosis.

In the emerging evidence presented and discussed in this communication, niacin presents a new opportunity for the development of a drug that hits both dyslipidemia, ASCVD and potentially NAFLD by mitigating all 3 major stages of NAFLD (steatosis, inflammation, and fibrosis). Because of its unique mechanisms of action (discussed below), niacin offers an excellent opportunity for an attractive, cost-saving and clinically available drug for combination with other drugs in development for incremental efficacy.

## Niacin for NASH/NAFLD: Current Evidence

### *In-vivo* pre-clinical evidence

To address the potential use of niacin for NAFLD, studies conducted in our laboratory utilized well established high-fat (western diet) diet fed rat model of NAFLD. We

showed that the addition of niacin in the diet significantly reduced liver fat content and prevented hepatic steatosis [12]. Additional studies indicated that niacin treatment to rats with preexisting steatosis induced by high-fat diet significantly regressed hepatic steatosis [12]. Furthermore, results from these studies also showed that niacin treatment significantly inhibited hepatic mRNA expression and activity of DGAT2 without affecting fatty acid synthesis and oxidation enzymes [12]. These data suggest that niacin’s action on inhibiting DGAT2, a terminal and committed enzyme for triglyceride synthesis, may be one of the major mechanisms of action of niacin to reduce hepatic steatosis in rats fed high fat diet.

Using GPR109A (niacin receptor)-knock out mice fed high-fat diet, recently Ye and colleagues have shown that niacin through activation of GPR109A ameliorated hepatic steatosis, potentially via PKC-ERK1/2-AMPK-mediated signaling pathways [13]. It is unclear whether this can apply to human disease as there is lack of GPR109A expression in the liver [24].

In addition to the effect of niacin on reducing NAFLD, studies from Li and associates have shown that niacin also attenuated chronic alcohol-induced fatty liver in rats [14], thus potentially extending the use of niacin in this disorder.

The potential use of niacin as an anti-fibrotic agent has been tested in chronic thioacetamide-induced liver fibrosis in rats. In this study, Arauz and colleagues have shown that niacin markedly prevented liver fibrosis induced by chronic administration of thioacetamide in rats [15]. Regression of fibrosis was not reported. Evidence indicated that the mechanism was reduction of oxidative stress. Notably, there is no published study on niacin’s effect on fibrosis regression. This is important, as such drugs will be expected to be especially useful for decreasing the hepatic fibrosis/collagen load thus alleviating cirrhosis and reduction of portal hypertension, underlying cause of acute fatal complications including variceal hemorrhage.

### *In-vitro* pre-clinical evidence

To extend *in-vivo* studies and to understand potential mechanisms of action, we utilized human primary hepatocytes, human hepatoblastoma cell line (HepG2 cells) and human hepatic stellate cells. Data from these studies showed that pharmacologically relevant concentrations of niacin significantly reduced fat accumulation induced by palmitic acid [16]. This inhibitory action of niacin on hepatocyte fat accumulation was associated with inhibition of diacylglycerol acyltransferase 2 (DGAT2), a key committed enzyme in triglyceride synthesis [16].

Since oxidative stress with increased reactive oxygen species (ROS) and lipid peroxidation products play a crucial role in hepatic inflammation and progression to NASH, we further investigated the effect of niacin on ROS production in human hepatocytes and stellate cells. We have shown that niacin significantly attenuated hepatocyte ROS production [16]. Furthermore, data indicated that niacin inhibited the activity of NADPH oxidase, a key enzyme involved in ROS production and oxidative stress [16]. Additional studies showed that niacin significantly decreased IL-8, one of the major pro-inflammatory mediators implicated in hepatic inflammation [16]. Using human neutrophils, data from our previous studies showed that niacin significantly inhibited myeloperoxidase (MPO), a major inflammatory mediator associated with NASH and hepatic inflammation [17].

In preliminary studies, recently we have shown that treating human primary stellate cells from normal subjects with pharmacologically relevant concentrations of niacin prevented stellate cell fibrosis (collagen type 1 and Sirius Red staining) induced by TGF- $\beta$  or oxidative stress mediator hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), major physiological stimulators of liver fibrosis [18].

### Clinical trial evidence

In support of the above discussed pre-clinical evidence, in a small uncontrolled clinical trial Hu and associated showed that treatment of dyslipidemia in 39 patients with Niacin Extended-Release (trade name Niaspan) for 23 weeks significantly reduced liver fat content (47%) and visceral fat (16%). Importantly, significant decreases from baseline in liver enzymes ALT, GGT, alkaline phosphatase, and inflammatory marker high sensitivity C Reactive Protein (CRP) were also observed [19]. It was also shown that the DGAT2 variant alleles were associated with a smaller reduction in liver fat content in response to niacin after adjustment for other covariates.

### Mechanism of Action on Steatosis, Inflammation, and Fibrosis

Available evidence generated in our laboratory and others suggest two major mechanisms of action by which niacin affects NAFLD and its complications including steatosis, hepatic inflammation, and fibrosis.

#### Role of niacin in hepatic triglyceride synthesis and steatosis

In liver, fatty acid synthesis and/or its availability for triglyceride synthesis and subsequent development of hepatic steatosis are mainly regulated by 3 mechanisms: (a), formation of long chain fatty acids from acetate via *de*

*novo* lipid synthesis (DNL) and (b), fatty acid mobilization from adipose tissue and (c), fatty acid generation via chylomicron lipolysis after a fatty meal and VLDL lipolysis in the fasting state. Fatty acids are then converted to diglycerides through esterification of fatty acids. DGAT2, a terminal and committed enzyme, converts diglycerides to TG. Excessive hepatic fatty acid formation (hallmark of steatosis) through any of the above pathways may result in TG deposited in liver and development of steatosis.

Studies from our laboratory showed that niacin inhibits DGAT2 isolated from microsomes from human HepG2 cells [20]. Additionally, Niacin also inhibits DGAT2 mRNA in human hepatocytes stimulated by free fatty acids [16] and liver tissue taken from rats fed a high fat diet in a model of NAFLD [12]. Furthermore, in a pilot clinical trial in patients with dyslipidemia DGAT2 variant alleles were associated with a smaller reduction in liver fat content in response to niacin after adjustment for other covariates [19]. The evidence strongly suggests that niacin-mediated inhibition of DGAT2 appears to be a major mechanism of action to beneficially affect liver triglyceride synthesis and steatosis. Additional/alternate mechanisms are also possible. Recent reports indicate that niacin, via increased levels of NAD<sup>+</sup> increases sirtuin 1 which is known to destabilize SREBPs thereby decreasing lipid synthesis in liver [21].

In older literature, niacin was shown to inhibit adipose tissue fatty acid mobilization [22] which later appeared to be mediated through GPR109A receptor (HCA2). Using GPR109A-knock out mice fed high-fat diet, recent work indicated that niacin through activation of GPR109A ameliorated hepatic steatosis [13]. Although such mechanism may have some effects on liver triglyceride accumulation, GPR109A agonists developed to act on this receptor do reduce fatty acid mobilization like niacin in humans but do not affect plasma TG or other lipids [23]. This indicates that this mechanism of action of niacin may not be important in explaining its anti-steatosis effect. Also, GPR 109A is not expressed in human liver tissue [24].

Importantly, by inhibiting TG synthesis from all 3 fatty acid sources, niacin differentiates from other drugs that attempt to decrease steatosis by *de novo* Lipid Synthesis. Drugs inhibiting fatty acid synthesis (e.g. Acetyl Co-A Carboxylase [ACC inhibitors]) will decrease *de novo* fatty acid synthesis, but TG synthesis is not inhibited because fatty acids from adipose tissue mobilization and chylomicron or VLDL lipolysis remain available. Recently reported clinical data on an ACC inhibitor showed no change or even an increase in plasma TG levels (and ASCVD risk) in patients treated with an ACC inhibitor [25].

## Role of niacin in oxidative stress and its impact on hepatic inflammation and fibrosis

Oxidative stress mediators including reactive oxygen species (ROS) and lipid peroxidation products have been implicated in the progression of NAFLD and its progressive form NASH with hepatic inflammation, fibrosis, and cirrhosis [26,27]. Lipid peroxidation products can activate transcription factors NF- $\kappa$ B and AP-1 in patients with NAFLD [28], key transcription factors that regulate the expression of several proinflammatory cytokines and hepatic inflammation. Emerging evidence indicates that ROS play an important role in liver stellate cell activation and progression to fibrosis [29,30]. Specifically, ROS stimulates the production of stellate cell collagen type 1 resulting in liver fibrosis through mediating intracellular signaling of the fibrogenic actions of TGF- $\beta$  [29,30].

In series of studies, we have shown that niacin markedly reduces oxidative stress in several cellular types including human hepatocytes, liver stellate cells, aortic endothelial cells, and neutrophils, [16-18,31]. Our data suggest that niacin through increasing cellular redox state (with increased NADPH and GSH levels) reduces cellular oxidative stress and subsequent inflammatory responses in various cell types. Our data suggest that niacin-mediated reduction in ROS may be a major mechanism by which niacin inhibit the activation of hepatic cells (e.g., hepatocytes and stellate cells) which in turn reduces hepatic inflammation, TGF- $\beta$  expression, collagen type-I deposition and fibrosis. In support of our *in-vitro* observation, Arauz and colleagues have shown that niacin markedly reduced liver fibrosis induced by chronic administration of thioacetamide in rats [15]. It was further shown niacin, through anti-oxidant properties and reducing TGF- $\beta$  expression, prevented hepatic fibrosis in this animal model [15]. Fibrosis regression was not reported.

## Clinical Considerations in the Use of Niacin

Pharmacologic doses of niacin for clinical treatment of dyslipidemia are in the range of 1500-2000 mg daily and can be increased to 3000 mg in some patients. Crystalline niacin must be given 3-4 times a day in divided doses. A major adverse effect is flushing. To mitigate this flushing, an extended-release formulation was developed over 20 years ago to reduce flushing and yet safe and effective as crystalline niacin and to be given once daily (trade name Niaspan, now generically called Niacin ER). It has been extensively researched and the only niacin formulation approved by the FDA (in USA) for treatment of dyslipidemia (including lowering LDL-Cholesterol, Triglycerides), and secondary prevention of myocardial infarction and

slowing atherosclerosis progression when combined with bile-acid sequestering LDL-C lowering therapy (package insert, Niaspan). Its safety has been extensively documented [32]. Although hyperglycemia is seen in some patients, it is generally controllable or normalizes. A recent extensive metanalysis of randomized trials including over 2000 patients showed no significant change in glucose or Hemoglobin A1c with niacin treatment [33]. Niacin ER is available by prescription only. It is given once at bedtime starting with a low dose (e.g. 500 mg) and titrated upward to a target of 2000 mg. With proper instructions to the patient, it is well tolerated. It should be noted that niacin is also available as other preparations over-the-counter (OTC), but these have not been tested for safety or efficacy and some preparations can be harmful [1]. Importantly, Niacin ER is not yet approved as an indication by the FDA for treatment of NAFLD because of lack of an approvable clinical trial data as discussed below.

Niacin offers an excellent opportunity for potential combination with other drugs in development. The reasons for this are that its unique mechanisms of action and its efficacy on all 3 major stages of NAFLD (steatosis, inflammation, and fibrosis) will yield synergistic incremental efficacy. Recent research shows that reduction of oxidative stress is a major mechanism for reversing steatohepatitis [12,16] and preventing fibrosis as shown in mice by Arauz et al. [15]. Niacin inhibits DGAT2 [12,16,20] which reduces steatosis which is necessary for downstream NASH and then fibrosis. Thus, niacin's efficacy on fibrosis (most important predictor of cirrhosis) is both direct and indirect. Currently there are more than 2 dozen targets (enzymes, receptors) for drug development. In the forefront are the FXR agonists, ACC inhibitors, CCR2/5 inhibitor, THR- $\beta$  agonists, SCD1 inhibitor, FGF 19 and 21 inhibitors, GLP-1 agonists, DPP-4 inhibitors, and others [5]. Most of these drugs can be potentially used in combination with niacin.

## Future Directions

The great advantage of niacin for a new repurposed treatment for NASH/NAFLD is that it has a long history of use in treatment of dyslipidemia and in ASCVD. Many of patients with atherogenic dyslipidemia have concurrent NAFLD. As indicated above, a safe and effective formulation is available. Niacin ER has been used in major cardiovascular trials in patients who had obesity, diabetes, dyslipidemia which are known risk factors for NASH. No liver toxicity or unexpected adverse effects were seen. Although this suggests that niacin ER may be safe in NASH patients, a clinical trial will be essential to confirm its safety. This would be followed by phase 2 and 3 randomized double-blind, placebo controlled trials with a larger number of patients to assess its efficacy for

resolution of NASH and/or reduction of fibrosis by liver biopsy with extended follow up to determine clinical benefit in reduction of portal hypertension and cirrhosis clinical outcomes.

Because niacin offers an opportunity for combination therapy, the phase 2 trials using the combination would also require studies on drug-drug interaction followed by assessing the combination against each drug in separate arms and subsequent phase 3 trial.

## Conclusion

Emerging preclinical and preliminary clinical evidence indicates that niacin (not as a vitamin, but as a drug), is a potential therapeutic agent for the treatment of nonalcoholic fatty liver disease and its complications of steatosis, steatohepatitis, and fibrosis. This is a novel repurposed use of a drug that is well known for its efficacy for over half a century, for atherogenic dyslipidemia and prevention of heart disease and stroke, pathologic conditions that occur concurrently in many NAFLD patients. Because of its unique mechanisms of action by reduction of oxidative stress and inhibition of hepatic diacylglycerol acyl transferase 2 (DGAT2) and increasing NAD<sup>+</sup> and sirtuin 1, it is an attractive cost-saving potential candidate for combination with another drug in development for increased efficacy for NAFLD. Clinical trials are warranted.

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## References

1. Kamanna VS, Ganji SH, Kashyap ML. Recent advances in niacin and lipid metabolism. Current Opinion in lipidology. 2013 Jun 1;24(3):239-245.
2. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. New England Journal of Medicine. 2001 Nov 29;345(22):1583-1592.
3. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. New England Journal of Medicine. 1990 Nov 8;323(19):1289-1298.

4. Kashyap ML, Ganji S, Nakra NK, Kamanna VS. Niacin for treatment of nonalcoholic fatty liver disease (NAFLD): novel use for an old drug?. Journal of Clinical Lipidology. 2019 Nov 1;13(6):873-879.

5. Neuschwander-Tetri BA. Pharmacologic management of nonalcoholic steatohepatitis. Gastroenterology & Hepatology. 2018 Oct;14(10):582-589.

6. Genfit Press Release, May 11, 2020: Announces results from interim analysis of RESOLVE-IT phase 3 trial of Elafibranor in adult patients with NASH and fibrosis.

7. Harrison SA, Wong VW, Okanoue T, Bzowej N, Vuppalanchi R, Younes Z, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: results from randomized Ph III STELLAR trials. Journal of Hepatology. 2020 Mar 6; 73:26-39

8. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology. 2018 May;67(5):1754-1767.

9. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. The Lancet. 2015 Mar 14;385(9972):956-965.

10. Potte W, Siddiqui MS, Sanyal AJ. Vascular disease in patients with nonalcoholic fatty liver disease. Seminars in Thrombosis and Hemostasis. 2015 Jul; 41(05):488-493.

11. Corey KE, Chalasani N. Management of dyslipidemia as a cardiovascular risk factor in individuals with nonalcoholic fatty liver disease. Clinical Gastroenterology and Hepatology. 2014 Jul 1;12(7):1077-1084.

12. Ganji SH, Kukes GD, Lambrecht N, Kashyap ML, Kamanna VS. Therapeutic role of niacin in the prevention and regression of hepatic steatosis in rat model of nonalcoholic fatty liver disease. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2014 Feb 15;306(4):G320-27.

13. Ye L, Cao Z, Lai X, Shi Y, Zhou N. Niacin ameliorates hepatic steatosis by inhibiting de novo lipogenesis via a GPR109A-mediated PKC-ERK1/2-AMPK signaling pathway in C57BL/6 mice fed a high-fat diet. The Journal of Nutrition. 2020 Apr 1;150(4):672-684.

14. Li Q, Xie G, Zhang W, Zhong W, Sun X, Tan X, et al. Dietary nicotinic acid supplementation ameliorates

chronic alcohol-induced fatty liver in rats. *Alcoholism: Clinical and Experimental Research. 2014 Jul;38(7):1982-92.*

15. Arauz J, Rivera-Espinoza Y, Shibayama M, Favari L, Flores-Beltrán RE, Muriel P. Nicotinic acid prevents experimental liver fibrosis by attenuating the prooxidant process. *International Immunopharmacology. 2015 Sep 1;28(1):244-251.*

16. Ganji SH, Kashyap ML, Kamanna VS. Niacin inhibits fat accumulation, oxidative stress, and inflammatory cytokine IL-8 in cultured hepatocytes: Impact on non-alcoholic fatty liver disease. *Metabolism. 2015 Sep 1;64(9):982-90.*

17. Ganji SH, Kamanna VS, Kashyap ML. Niacin decreases leukocyte myeloperoxidase: mechanistic role of redox agents and Src/p38MAP kinase. *Atherosclerosis. 2014 Aug 1;235(2):554-61.*

18. Kashyap ML, Kamanna S, Hoa N, Kamanna VS. New Use of Niacin for the Potential Treatment of Nonalcoholic Fatty Liver Disease (NAFLD): Efficacy on Fibrosis. *AASLD Industry Colloquium: Novel targets and therapies in liver disease, Washington DC, January 19-20, 2018.*

19. Hu M, Chu WC, Yamashita S, Yeung DK, Shi L, Wang D, et al. Liver fat reduction with niacin is influenced by DGAT-2 polymorphisms in hypertriglyceridemic patients. *Journal of Lipid Research. 2012 Apr 1;53(4):802-809.*

20. Ganji SH, Tavintharan S, Zhu D, Xing Y, Kamanna VS, Kashyap ML. Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. *Journal of Lipid Research. 2004 Oct 1;45(10):1835-1845.*

21. Romani M, Hofer DC, Katsyuba E, Auwerx J. Niacin: an old lipid drug in a new NAD<sup>+</sup> dress. *Journal of Lipid Research. 2019 Apr 1;60(4):741-746.*

22. Carlson LA. Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue in vitro. *Acta Medica Scandinavica. 1963;173:710-722.*

23. Lauring B, Taggart AK, Tata JR, Dunbar R, Caro L, Cheng K, et al. Niacin lipid efficacy is independent of both the niacin receptor GPR109A and free fatty acid suppression. *Science Translational Medicine. 2012 Aug 22;4(148):148.*

24. Tunaru S, Kero J, Schaub A, Wufka C, Blaukat A, Pfeffer K, et al. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nature Medicine. 2003 Mar;9(3):352-355.*

25. Kim CW, Addy C, Kusunoki J, Anderson NN, Deja S, Fu X, et al. Acetyl CoA carboxylase inhibition reduces hepatic steatosis but elevates plasma triglycerides in mice and humans: a bedside to bench investigation. *Cell Metabolism. 2017 Aug 1;26(2):394-406.*

26. Gawrieh S, Opara EC, Koch TR. Oxidative stress in non-alcoholic fatty liver disease: pathogenesis and antioxidant therapies. *Journal of Investigative Medicine 2004 Dec;52(8):506-14.*

27. Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. *American Journal of Gastroenterology 2004 Aug;99(8):1497-502.*

28. Videla LA, Tapia G, Rodrigo R, Pettinelli P, Haim D, Santibañez C, et al. Liver NF- $\kappa$ B and AP-1 DNA binding in obese patients. *Obesity. 2009 May;17(5):973-979.*

29. Liang S, Kisseleva T, Brenner DA. The role of NADPH oxidases (NOXs) in liver fibrosis and the activation of myofibroblasts. *Frontiers in Physiology. 2016 Feb 2;7:17.*

30. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology. 2008 May 1;134(6):1655-1669.*

31. Ganji SH, Qin S, Zhang L, Kamanna VS, Kashyap ML. Niacin inhibits vascular oxidative stress, redox-sensitive genes, and monocyte adhesion to human aortic endothelial cells. *Atherosclerosis. 2009 Jan 1;202(1):68-75.*

32. Anderson TJ, Boden WE, Desvigne-Nickens P, Fleg JL, Kashyap ML, McBride R, et al. Safety profile of extended-release niacin in the AIM-HIGH trial. *New England Journal of Medicine. 2014 Jul 17;371(3):288-290.*

33. Xiang D, Zhang Q, Wang YT. Effectiveness of niacin supplementation for patients with type 2 diabetes: A meta-analysis of randomized controlled trials. *Medicine. 2020 Jul 17;99(29) (e21235).*