

A review of pharmacological treatments of NASH

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption and affects up to a third of the population in many developed countries. Approximately 10-30% of patients with NAFLD will progress to non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury and inflammation resulting in progressive liver fibrosis, liver failure and liver cancer. The increase in the number of patients with advanced liver disease secondary to NASH, as well as associated hepatocellular carcinoma, will impact on the potential future demand for Liver Transplantation (LT) and also increase the cardiovascular mortality. Despite these large numbers of pharmacological agents that have been used to treat NASH, none of them have yet been shown to improve clinically meaningful outcomes. Also the long term safety of several agents remain to be established.

Conclusion: In this clinical review, we will briefly review the pharmacological treatment of NASH in the last years due to the increasing incidence of NAFLD and NASH around the world.

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Abbreviations: NAFLD, nonalcoholic fatty liver disease; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; IR, insulin resistance; UDCA, ursodeoxycholic acid; GLP-1, glucagon-like peptide-1; LOXL 2, lysyl oxidase-like 2

Introduction

Nonalcoholic fatty liver disease (NAFLD) is recognize as the most common cause of chronic liver disease, and is estimated to affect 30% of adults and 10% of children in United States.¹ NASH is associated with a significant increase in liver-related mortality as well as cardiovascular mortality, progressive liver fibrosis and ultimately cirrhosis.²⁻¹⁰ NASH comes from data obtained from patients with the diagnosis of cryptogenic cirrhosis, which accounts for about 10% of liver transplants. The increase in the number of patients with advanced liver disease secondary to NASH, as well as associated hepatocellular carcinoma, will impact on the potential future demand for Liver Transplantation (LT).¹¹ Management of patients with NAFLD depends largely on the stage of disease, emphasising the importance of careful

risk stratification. All patients with NAFLD require advice about lifestyle modification aimed at weight loss and increased physical activity, as well as treatment of any associated metabolic risk factors (diabetes, hypertension and dyslipidaemia).¹² Since the majority of patients suffer from obesity, insulin resistance (IR) and concomitant cardiovascular disease, weight reduction of approximately 10% has been advised by the American Gastroenterological Association.¹³ Due to the metabolic risk factors that are common to both NAFLD/NASH, cardiovascular disease and progression of disease, therapeutic options in NAFLD and NASH are currently limited mainly to interventions in terms of diet and lifestyle. A medication with long-term effectiveness that would beneficially affect reduce the risk does currently not exist until now. In this clinical review, we will also briefly review the lifestyle modification and the pharmacological treatment of NASH from last years. While a medication with long-term effectiveness that would reduce the risk at liver related outcomes currently does exist, several therapeutics agents appear to look very promising. The used such agents will be discussed (Table 1).

Table 1 Summary of management of NAFLD/NASH

| Treatment | Intervention/Indication | Target/Outcome |
|----------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Lifestyle modification | Exercise/Diet | >7% loss of body weight reduces steatosis, ballooning and hepatic inflammation. ¹⁷ |
| Weight loss drugs (enteric lipase inhibitor) | Inhibit enteric lipid absorption | No histologic changes have been demonstrated. ^{16,18} |
| Vitamin E | Nondiabetic patients with only biopsy-proven NASH | Improvement in steatosis, inflammation, and ballooning ^{17,18} |
| Thiazolidinediones (Pioglitazone) | Patients with NASH | Improvement in steatosis and inflammation and reduced fibrosis progression. ^{37,39} |
| Statins | NAFLD patients with dyslipidaemia | Benefit in terms of cardiovascular morbidity and mortality. ⁴⁹ |

Lifestyle modification

Lifestyle changes associated with weight reduction results in the loss of white adipose tissue, which decreases IR. Exercise can also improve muscular insulin sensitivity, which may improve the impact of IR on NAFLD.^{14,15} Several studies have shown a reduction

in transaminases as well as histology-determined steatosis grade and inflammation in patients with NASH who had significant weight loss.^{16,17} The most effective treatment consists of weight reduction and intensive lifestyle modification with an increase in physical activity/exercise, which has been confirmed to be able to improve histological results.¹⁸ Although the optimum exercise to treat NAFLD is not

known, studies examining moderate intensity training, high intensity training and resistance exercise have shown improvement in liver enzymes and reduction in liver fat, independent of weight loss, but the effects on histology remain unknown.^{19,19-21} The best evidence for weight loss as a means to improve liver histology in NASH comes from a trial that randomized 31 obese persons with NASH to intensive lifestyle. The intensive weight loss group improved steatosis, necrosis and inflammation, but not fibrosis. Importantly, participants with more than 7% weight loss had significant improvement in steatosis, lobular inflammation, ballooning, and NAFLD Activity Score (NAS).¹⁷

Weight loss drugs

Orlistat inhibit enteric lipid absorption and has been associated with weight loss. In a recent trial, patients taking orlistat did not benefit from significant weight loss or histological improvement compared with the placebo group. Probably, the improvement was proportional to weight loss and not directly by the use of the drug. Another randomized control study to investigate the effects of orlistat showed that orlistat was safe and well tolerated, although, no histologic changes have been demonstrated. There are no evidence supporting the efficacy of orlistat in patients with NASH.^{16,22}

NASH specific therapies

For patients with biopsy-proven NASH and also are at highest risk of developing progressive liver disease, more aggressive lifestyle modification and pharmacotherapy are required.

Vitamin E

The lipotoxicity model in NASH attributes a central role to oxidative stress in the progression of disease in patients with NASH.²³ The Vitamin E in a large multi-center, randomised controlled trial demonstrating improvements in all histological parameters, except fibrosis score.²⁴⁻²⁸ In the large PIVENS trial, significantly more patients had improvement in steatohepatitis following 96 weeks of vitamin E 800 IU/day compared with placebo in patients without diabetes (42% vs 19% $p < 0.001$).²⁹ This was confirmed in a study of childhood NASH, where vitamin E was shown to reduce steatohepatitis in a subgroup who had follow-up liver biopsies.³⁰ The vitamin E causes improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in adults with NASH, however no effect on hepatic fibrosis. And is also associated with a decrease in aminotransferases in subjects with NASH.^{17,31} The recent NAFLD guideline recommends Vitamin E as a first-line treatment for nondiabetic patients with only biopsy-proven NASH.³²⁻³⁴ Others agents with antioxidant properties (e.g., N-acetylcysteine, vitamin C, probucol, betaine) have not been shown to be effective in treating NASH.^{19,35} In addition, an initial open-label studies of ursodeoxycholic acid (UDCA), a potential cytoprotective agent in NAFLD, it was not significantly different in terms of liver biochemistries or histology when compared with placebo.^{19,36}

Drugs targeting insulin resistance

Thiazolidinediones and metformin

A meta-analysis has determined that metformin does not have a beneficial impact on transaminase levels or liver histology, and promising early results are probably attributable to lifestyle intervention in the treatment groups.^{37,38} Another study concluded that 6-12 months of metformin plus lifestyle intervention did not improve aminotransferases or liver histology, compared with lifestyle intervention alone, independently of metformin dose or the presence of diabetes.³⁷ Several studies investigated the effect of pioglitazone

and rosiglitazone on aminotransferases and liver histology in adults with NASH. Thiazolidinediones have been trialed showing some improvement in steatosis and inflammation and reduced fibrosis progression.^{37,39} A recent meta-analysis has demonstrated that pioglitazone treatment in NASH significantly improves steatosis, inflammation and to a lesser degree fibrosis.³⁷ Treatment with pioglitazone is associated with weight gain²⁷ and there have been reports of increased risk of congestive cardiac failure,^{40,41} bladder cancer⁴² and reduced bone densit.⁴³ In the case of rosiglitazone, increased risk of myocardial infarction.⁴⁴

GLP-1 analogues

Studies with Glucagon-like peptide-1 (GLP-1) analogues (such as liraglutide or exenatide) are underway to determine the effect of liraglutide on liver histology. However, there is recent evidence to suggest that GLP-1 agonists might induce pancreatitis (particularly in those with very high triglycerides) and increase the potential for pancreatic cancer.⁴⁵

Hypolipidemia drugs

Atherogenic dyslipidemia is related to increased insulin-induced hepatic lipid synthesis in patients with NAFLD and also high-normal level of ALT was associated with higher levels of Low-density lipoproteins (LDL-cholesterol), LDL particle concentration (LDL-P), size, small dense LDL-cholesterol (sdLDL-C), and sdLDL particles ($P < .001$ for all).^{46,47} Non-high-density lipoprotein cholesterol (non-HDL-C) is a stronger predictor for NAFLD than total cholesterol, low-density lipoprotein cholesterol, triglycerides and HDL. No patients with non-HDL-C < 130 mg/dl developed NAFLD, whereas 20.8% of those with values between 130 to 160 and 24.6% of those with values > 160 mg/dl developed NAFLD (p for trend = 0.015).⁴⁸ Statins are safe to recommend in NAFLD patients with dyslipidaemia. They do confer a benefit in terms of cardiovascular morbidity and mortality.^{16,49} Raised transaminases are frequently seen in patients receiving statins and serious liver injury is rarely seen in clinical practice.¹⁶

Angiotensin II receptor blocker

A previous study has shown the use of telmisartan, an angiotensin II receptor blocker (ARB) with PPAR- γ -modulating activity, improved transaminase levels and insulin sensitivity, and showed a significant decrease in NASH activity score and fibrosis.⁵⁰ Another ARB, losartan, induced a significant reduction in serum fibrosis markers and numbers of activated hepatic stellate cell in 48 weeks [51,52]. There is no sufficient evidence to support the use of these medications as specific treatments for NAFLD, although the aggressive management of cardiovascular risk factors is recommended.⁵³

Extracts/phytochemicals/polyherbal formulations

Available scientific information and experiments on antiobesity and antidiabetic plant extracts/phytochemicals/polyherbal formulations greatly outnumber the preclinical and clinical studies conducted on NASH so far. Natural products of herbal origin have been extensively reported to prevent hepatic lipid accumulation without exhibiting major side effects. There are insufficient evidence to support the use of Herbal Medicines as treatment for NAFLD/NASH.⁵⁴ Retrospective studies suggest that coffee consumption may exert beneficial effects in patients with NAFLD. No association was demonstrated between coffee consumption and the new onset of NAFLD, but coffee intake may exert beneficial effects on fibrosis progression.⁵⁵ Owing to these reasons, determination of toxicity dosage of any herbal preparation through preclinical acute and sub chronic toxicity evaluations becomes necessary.

Omega-3 fatty acids, pentoxifylline and probiotics

Other regimens such as omega-3 fatty acids, pentoxifylline and probiotics have been studied for treatment of NASH⁵⁰. Fish oil is composed primarily of omega-3 fatty acids, which, along with omega-6 fatty acids, constitute the essential fatty acids. A recent meta-analysis on the use of omega 3 polyunsaturated fatty acid (PUFA) on NASH showed a beneficial changes in liver fat for those receiving PUFA treatment as well as an observed reduction in AST, but the optimal dose is not currently known⁶¹. Pentoxifylline is considered as anti-TNF compound. Although one study suggested improvement in steatosis, there are lack of histological and laboratory outcomes.^{56,57} Probiotics have been suggested to be beneficial in NASH by augmenting the microbial environment in the intestine. At present, there are no evidence to support the use of any of these regimens for patients with NASH.⁵⁸ Omega-3 fatty acids, pentoxifylline, and probiotics cannot be recommended as first-line therapeutic agents to treat NASH.

Anti-fibrotic

Ongoing trials with a monoclonal antibody against lysyl oxidase-like 2 (LOXL2), in subjects with advanced liver fibrosis but not cirrhosis secondary to NASH.

Conclusion

NAFLD is among the most common causes of chronic liver disease worldwide and can potentially progress to cirrhosis, liver failure and hepatocellular carcinoma. A multidisciplinary approach using lifestyle modifications and optimizing metabolic risk factors is still the best option. The available treatment options for NASH include weight loss, dietary and lifestyle modifications, use of insulin sensitizing, Vitamin E and lipid lowering drugs. Despite these large numbers of pharmacological agents that have been used to treat NASH, none of them have a specific and directly effect. In the near future, individualized therapy based on severity of disease and treatment response might be a reality.

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Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Wree A, Broderick L, Canbay A, et al. From NAFLD to NASH to cirrhosis-new insights into disease mechanisms. *Nat Rev Gastroenterol Hepatol*. 2013;10(11):627–636.
2. Matteoni CA, Younossi ZM, Gramlich T, et al. Non alcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology*. 1999;116(6):1413–1419.
3. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology*. 1990;12(5):1106–1110.
4. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140(1):124–131.
5. Wong VW, Wong GL, Choi PC, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut*. 2010;59(7):969–974.
6. Fassio E, Alvarez E, Domínguez N, et al. Natural history of non alcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. *Hepatology*. 2004;40:820–826.
7. Adams LA, Sanderson S, Lindor KD, et al. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol*. 2005;429(1):132–138.
8. Ong J, Younossi ZM, Reddy V, et al. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl*. 2001;7(9):797–801.
9. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937–952.
10. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;363(14):1341–1350.
11. Newsome PN, Allison ME, Andrews PA, et al. British Transplant Society. Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. *Gut*. 2012;61(4):484–500.
12. Anstee QM, McPherson S, Day CP. How big a problem is non-alcoholic fatty liver disease? *BMJ*. 2011;343:d3897.
13. Sabuncu T, Nazligul Y, Karaoglanoglu M, et al. The effects of sibutramine and orlistat on the ultrasonographic findings, insulin resistance and liver enzyme levels in obese patients with non-alcoholic steatohepatitis. *Rom J Gastroenterol*. 2003;12(3):189–192.
14. Adams LA, Zein CO, Angulo P, et al. A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2004;99(12):2365–2368.
15. Kadayifci A, Merriman R, Bass N. Medical treatment of non-alcoholic steatohepatitis. *Clin Liver Dis*. 2007;11(1):119–140.
16. Harrison SA, Fecht W, Brunt EM, et al. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. *Hepatology*. 2009;49(1):80–86.
17. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology*. 2010;51(1):121–129.
18. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. *Hepatology*. 2008;48(6):1791–1798.
19. Attar B, Van Thiel DH. Current concepts and management approaches in non alcoholic fatty liver disease. *Scientific World Journal*. 2013;2013:481893.
20. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *J Hepatol*. 2012;56(1):255–266.
21. Hallsworth K, Fattakhova G, Hollingsworth KG, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut*. 2011;60(9):1278–1283.
22. Zelber-Sagi S, Kessler A, Brazowsky E, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2006;4(5): 639–644.
23. Salomone F, Li Volti G, Rosso C, et al. Unconjugated bilirubin, a potent endogenous antioxidant, is decreased in patients with non-alcoholic steatohepatitis and advanced fibrosis. *J Gastroenterol Hepatol*. 2013;28(7):1202–1208.
24. Hasegawa T, Yoneda M, Nakamura K, et al. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with nonalcoholic steatohepatitis: a pilot study. *Aliment Pharmacol Ther*. 2001;15(10):1667–1672.

25. Harrison SA, Torgerson S, Hayashi P, et al. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2003;98(11):2485–2490.
26. Dufour JF, Oneta CM, Gonvers JJ, et al. Swiss Association for the Study of the Liver. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2006;4(12):1537–1543.
27. Sanyal AJ, Mofrad PS, Contos MJ, et al. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2004;2(12):1107–1115.
28. Yakaryilmaz F, Gulter S, Savas B, et al. Effects of vitamin E treatment on peroxisome proliferator-activated receptor- α expression and insulin resistance in patients with non-alcoholic steatohepatitis, results of a pilot study. *Intern Med J*. 2007;37(4):229–235.
29. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, et al. (2010) Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 362(18):1675–1685.
30. Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA*. 305(16):1659–1668.
31. Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142(1):37–46.
32. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005–2023.
33. Pathil A, Mueller J, Warth A, et al. Ursodeoxycholy lysophosphatidylethanolamide improves steatosis and inflammation in murine models of nonalcoholic fatty liver disease. *Hepatology*. 2012;55(5):1369–1377.
34. Musso G, Anty R, Petta S. Antioxidant therapy and drugs interfering with lipid metabolism: could they be effective in NAFLD patients? *Curr Pharm Des*. 2013;19(29):5297–5313.
35. Musso G, Gambino R, Cassader M, et al. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology*. 2010;52(1):79–104.
36. Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *Hepatology*. 2004;39(3):770–778.
37. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34(3):274–285.
38. Ratzliff V, Giral P, Jacqueminet S, et al. Rosiglitazone for nonalcoholic steatohepatitis: One-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology*. 2008;135(1):100–110.
39. Promrat K, Lutchman G, Uwaifo GI, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology*. 2004;39(1):188–196.
40. Boettcher E, Csako G, Pucino F, et al. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2012;35(1):66–75.
41. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet*. 2007;370(9593):1129–1136.
42. Piccinni C, Motola D, Marchesini G, et al. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care*. 2011;34(6):1369–1371.
43. Lecka-Czernik B. Bone loss in diabetes: use of antidiabetic thiazolidinediones and secondary osteoporosis. *Curr Osteoporos Rep*. 2010;8(4):178–184.
44. Cusi K, Orsak B, Lomonaco R, et al. Extended treatment with pioglitazone improves liver histology in patients with prediabetes or type 2 diabetes mellitus and NASH. *Hepatology*. 2013;58:248A.
45. Nauck MA. A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. *Diabetes Care*. 2013;36(7): 2126–2132.
46. Siddiqui MS, Fuchs M, Idowu MO, et al. Severity of Nonalcoholic Fatty Liver Disease and Progression to Cirrhosis Associate With Atherogenic Lipoprotein Profile. *Clin Gastroenterol Hepatol*. 2014;13(5):1000e3–1008e3.
47. Siddiqui MS, Sterling RK, Luketic VA, et al. Association Between High-Normal Levels of Alanine Aminotransferase and Risk Factors for Atherogenesis. *Gastroenterology*. 2013;145(6):1271 e1-3-1279e1-3.
48. Zelber-Sagi S, Salomone F, Yeshua H, et al. Non-high-density lipoprotein cholesterol independently predicts new onset of non-alcoholic fatty liver disease. *Liver Int*. 2014;34(6):e128–e135.
49. Chalasani N, Aljadhey H, Kesterson J, et al. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology*. 2004;126(5):1287–1292.
50. Georgescu EF, Ionescu R, Niculescu M, et al. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. *World J Gastroenterol*. 2009;15(8): 942–954.
51. Yokohama S, Yoneda M, Haneda M, et al. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology*. 2004;40:1222–1225.
52. Yokohama S, Tokusashi Y, Nakamura K, et al. Inhibitory effect of angiotensin II receptor antagonist on hepatic stellate cell activation in non-alcoholic steatohepatitis. *World J Gastroenterol*. 2006;12(2):322–326.
53. Day CP. Clinical spectrum and therapy of non-alcoholic steatohepatitis. *Dig Dis*. 2012;30Suppl1:69–73.
54. Jadeja R, Devkar RV, Nammi S. Herbal Medicines for the Treatment of Nonalcoholic Steatohepatitis: Current Scenario and Future Prospects. *Evid Based Complement Alternat Med*. 2014:648308.
55. Zelber-Sagi S, Salomone F, Webb M, et al. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. *Transl Res*. 2014;165(3):428–436.
56. Parker HM, Johnson NA, Burdon CA, et al. Omega-3 supplementation and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol*. 2012;56(4):944–951.
57. Zein CO, Lopez R, Fu X, et al. Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. *Hepatology*. 2012;56(4):1291–1299.
58. Iacono A, Raso GM, Canani RB, et al. Probiotics as an emerging therapeutic strategy to treat NAFLD: focus on molecular and biochemical mechanisms. *J Nutr Biochem*. 2011;22(8):699–711.