Natural Products: New Hope for Nonalcoholic Steatohepatitis?

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NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is a spectrum of disorders characterized by hepatic lipid accumulation and cellular degeneration in the absence of significant alcohol consumption that may progress to non-alcoholic steatohepatitis (NASH), cirrhosis, or hepatocellular carcinoma (HCC).^{1,2} Owing in large part to the obesity epidemic,³ NAFLD is the most prevalent chronic liver disease and is projected to become the leading cause of liver transplantation. The rapidly growing NAFLD epidemic parallels the obesity trajectory and is estimated to be 25% in the general population, and increases to ~75% to 90% in patients with obesity or diabetes.⁴ Although simple nonalcoholic fatty liver (NAFL) in the absence of hepatocellular injury is generally benign and nonprogressive, ~30% of NAFL patients develop NASH that can further progress to cirrhosis, end-stage liver disease, and HCC.^{5,6} NAFLD patients exhibit increased morbidity and total mortality due to cardiovascular disease as well as liver-related complications compared with the general population.⁵

Although NASH is a major public health concern, there are currently no approved treatments. Recommended first-line therapy is lifestyle change, including physical activity and weight loss. Weight loss of 3% to 5%, whether through hypocaloric diet, exercise, or both, improves hepatic steatosis but not other features of NASH, whereas more substantial weight loss (~7%) is required to regress NASH, and 10% to improve fibrosis^{3,7}; however, compliance with the lifestyle changes necessary to accomplish and maintain weight loss is often challenging.^{5,8} Other therapeutic approaches focus on controlling concurrent metabolic disorders such as diabetes and hyperlipidemia.⁹ Antidiabetic drugs (e.g., metformin and pioglitazone), lipid-lowering drugs (e.g., statins and fibrates), antiobesity medication (e.g., orlistat), and antioxidants (e.g., vitamin E) may improve some metabolic parameters; however, they either have minimal effects on liver histology or have other adverse effects limiting their use.^{8,10,11}

Pharmacotherapy for NASH is under intense development, with >40 clinical programs underway. However, late-stage programs have thus far shown marginal efficacy and have troubling safety signals, suggesting the need for alternative approaches. In this issue of the journal, Mizrahi *et al.*¹² provide promising data demonstrating anti-inflammatory effects of *Hoodia* extracts (*Hesperaloe parviflora*), which result in marked improvements in chemically

induced immune hepatitis. They further show that *H. parviflora* improves glucose tolerance as well as hepatic triglycerides and liver histology in both genetic (*ob/ob* mice) and nutritionally induced (high-energy diets) models of NAFLD/NASH. Enthusiasm is tempered by lack of safety data, as another member of the genus (*Hoodia gordonii*) was shown to cause short-term changes in vital signs and some laboratory parameters.¹³ However, given the diversity of chemical composition among *Hoodia* spp., comparable safety signals cannot be presumed to be present in *H. parviflora*. Thus, these findings are cause for optimism, although there is much to be done, including identifying the bioactive component(s) and optimizing dosage, extending these findings to a high-fidelity translational model of NASH inflammation fibrosis, such as the AMLN or DIAMOND mouse models¹⁴ and, of course, clinical translation.

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