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SPECIAL ARTICLE

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A patient-centered approach to dietary supplements for patients with chronic liver disease

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Abstract

The use of dietary supplements by patients with chronic liver disease is prevalent and rising. Despite the known risks of dietary supplements, including hepatotoxicity, adulteration, and contamination, patients with chronic liver disease often turn to dietary supplements to support their liver and/or overall health but are not necessarily empowered with the information or guidance from their liver practitioner to do so. This article provides practitioners with a framework for balancing the risks and benefits of dietary supplements in patients with chronic liver disease, offering examples of independent resources and certifications to use this framework in clinical practice. We offer 3 common clinical scenarios to highlight how the use of this framework can improve communication and decision-making in clinical practice. By adapting principles from Integrative Medicine, this article advocates for a patient-centered approach to dietary supplements in patients with chronic liver disease, encouraging open dialogue between clinicians and their patients to facilitate informed decision-making and personalized care.

Keywords: dietary supplement, integrative medicine, liver health, patient-centered, shared decision-making

Abbreviations: DSHEA, Dietary Supplement Health and Education Act; EFSA, European Food Safety Authority; FDA, food and drug administration; MASLD, metabolic dysfunction–associated steatotic liver disease; NAC, *N*-acetyl-cysteine; NHANES, National Health and Nutrition Examination Survey; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, national institutes of health; PSC, primary sclerosing cholangitis.

According to the US Dietary Supplement Health and Education Act (DSHEA) of 1994 (Bill S.784), a dietary supplement is defined as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients."[1] The use of dietary supplements in the United States is high. Data from the National Health and Nutrition Examination Survey (NHANES) revealed that between 2017 and 2018, 58% of adults took at least 1 dietary supplement within the last 30 days; among adults over the age of 60 years, this proportion approaches 75%.[2,3] The use of dietary supplements is not isolated to patients *without* liver disease; in fact, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reported that up to 40% of patients attending liver clinics use dietary supplements (which may be an underestimate due to under-reporting).[4] Furthermore, the use of dietary supplements has increased in all adult age groups from the decade prior.[2]

With widespread access to information about dietary supplements to support "liver health," patients with chronic liver disease are increasingly seeking to integrate dietary supplements into their lives but are not necessarily empowered with the objective data they need to do so. In principle, the risks of dietary supplements are well known. These include liver toxicity due to adulteration, contamination, and/or the compounds themselves. These risks may be elevated for a patient with chronic liver disease due to decreased reserve to withstand any degree of DILI or impaired hepatic clearance. In practice, however, these risks can be challenging for patients to identify, especially given lax regulations around marketing, manufacturing, and monitoring of adverse events compared to pharmacologics. Furthermore, given that conventional therapies for chronic liver diseases are often limited (eg, primary sclerosing cholangitis [PSC] and metabolic dysfunction–associated steatotic liver disease [MASLD]), or associated with significant side effects (ie, autoimmune hepatitis), patients with chronic liver disease may be particularly eager to integrate dietary supplements into their lives to support their liver and overall health but may lack the support and guidance of a knowledgeable practitioner. Instead, the information they can access includes self-selected (and often positively biased) sources that include social media, podcasts, and influencers—in addition to targeted advertisements—that may encourage them to take a dietary supplement without consultation with a health care practitioner. In the past 2 decades, there has been increasing research on a wide range of dietary supplements to suggest that judicious use of certain supplements can be beneficial.[5–7] Given this context, the question may not be *whether* patients with chronic liver diseases should "be allowed" to take dietary supplements, but rather, *how* can we, as practitioners of hepatology care, engage our patients in an open discussion about their interest in taking dietary supplements and support them to make informed choices?

In this article, we explore this question. Specifically, we will adapt frameworks that originally emerged from Integrative Medicine, the field that brings together conventional with complementary medicine to health care in a coordinated way that emphasizes the person as a whole rather than 1 organ system (Whole Health model).[7] Integrative Medicine focuses on approaches to care that directly address health promotion and restoration, disease prevention, and/or symptom management[7]—common motivating factors for dietary supplement use. It is important to note that this article is not intended to persuade hepatology providers to "prescribe" dietary supplements as part of their practice. Rather, this article is intended to help broaden the perspective of clinicians who may be less familiar with this area and serve as a guide for providers who are open to considering dietary supplements within their practice along a spectrum—whether to counsel their patients who initiate the conversation about specific supplements or to actively recommend supplements to manage symptoms or as part of an integrative care plan to manage a patient's chronic liver disease.

POTENTIAL BENEFITS OF DIETARY SUPPLEMENTS IN PATIENTS WITH CHRONIC LIVER DISEASE

Examples of dietary supplements that are commonly used in hepatology are listed in Table 1.[8,9] Among these, only a handful have adequate data to support their benefits on objective liver-specific parameters

TABLE 1 Categories of dietary supplements and examples commonly used by patients with chronic liver disease and/or are marketed for "liver health"

Category	Specific examples of dietary supplements that are commonly used by patients with chronic liver disease
Vitamins	Vitamin D, vitamin E, multivitamin
Minerals	Calcium, zinc
Herbs and botanical	Milk thistle, turmeric, licorice root
Botanical compounds	Silymarin, curcumin, glycyrrhizin
Amino acids	Branched-chain amino acids, L-ornithine L-aspartate
Live microbials	Probiotics
Other	Fish oil, *S*-adenosylmethionine, *N*-acetyl-cysteine

(eg, biochemical response, fibrosis regression, portal hypertensive complications, and mortality) in patients with chronic liver disease. For example, vitamin E has been shown in many studies to reduce aminotransferases, a surrogate for disease activity in patients with metabolic dysfunction–associated steatohepatitis.[10,11] A Cochrane review of 16 trials concluded that there was "high-quality evidence" to support the beneficial effect of branched-chain amino acids on HE.[12] Meta-analyses have demonstrated that probiotics improve minimal HE, decrease hospitalization rates, and decrease progression to overt HE in patients with cirrhosis, although even these meta-analyses were limited by the heterogeneity of the probiotic formulations included in the studies.[13,14]

However, the outcomes that clinicians hold in the highest regard—such as aminotransferases and portal hypertensive complications—are not always what are most important to patients. We should respect the outcomes that patients value (eg, patient-reported outcomes), as they can serve to help us understand their underlying motivations for seeking to take dietary supplements. Although contemporary data on the reasons why patients specifically with chronic liver diseases take dietary supplements are lacking, NHANES data from US adults in the general population revealed that the primary motivations for the use of dietary supplements were to "improve overall health" (45%) or "maintain health" (33%).[15] Other top reasons (>20% adults reporting) were "for bone health," "to supplement the diet," and "to prevent health problems."[15] These reasons should not be dismissed. Patient-reported outcomes and underlying motivations for their health play a critical role in the selection of and adherence to therapeutic strategies. Multiple studies have demonstrated the powerful effects of patient engagement on meaningful outcomes, including treatment results, quality of care, patient adherence, and self-efficacy.[16,17]

POTENTIAL HARMS OF DIETARY SUPPLEMENTS IN PATIENTS WITH CHRONIC LIVER DISEASE

DILI from dietary supplements has been well described in the literature.[18,19] Most hepatologists have seen at least 1, if not a handful of patients who have experienced serious DILI, including those that have resulted in death or necessitated liver transplantation. For a patient with advanced liver disease, the stakes may be higher: supplement-induced liver injury, which would otherwise have been self-limited in patients without chronic liver disease, can precipitate hepatic decompensation in those with cirrhosis.

Harms from dietary supplements can result from a number of reasons (Table 2). According to data from the US Acute Liver Failure Study Group, the proportion of cases of severe liver injury attributable to herbal or dietary supplements (vs. other causes, such as acute viral hepatitis) was 21% (2007–2015)[30;] similarly, the proportion was 20% in 2013–2014 in the Drug-Induced Liver Injury network.[19] In a multicenter study that included nearly 1300 patients in India who presented with DILI from 2013 to 2018, 14% of cases of DILI were attributed to complementary and alternative medicines.[31] Data from the Spanish DILI registry reported that dietary supplements were responsible for 4% of cases of DILI.[32] More recently, there have been an increasing number of case reports of severe DILI from turmeric and ashwagandha,[24,33–37] paralleling global market trends of increasing use of these 2 supplements.[38,39]

TABLE 2 Factors contributing to increased risk of harm from dietary supplements

Factors	Examples
Contamination with external substances	Heavy metals (eg, arsenic, lead, and mercury) Mycotoxins, and aflatoxins in milk thistle[20,21]
Adulteration	Sildenafil in sexual enhancement supplements, sibutramine in weight loss supplements[22]
Taking concentrated forms of otherwise safe and commonly available botanical	Green tea extract from green tea[23] Curcumin, the bioactive compound of *Curcuma longa* (turmeric)[24]
Mislabeling of the dietary ingredient	Highest rate reported in supplements marketed for sexual enhancement, weight loss, and athletic performance enhancement[25–27]
The dietary compound itself	Aconite[28] and chaparral[29]

However, available data are largely limited to case reports, case series, or studies of patients presenting with DILI. Evaluating risk from only personal anecdotes or case series in the literature leads to inaccuracies in the assessment of the true risk of dietary supplements. This occurs in part because of the inability to track the total number of patients taking each supplement to accurately determine the denominator of patients underlying the cases, as was highlighted in a recent cohort series that analyzed real-world data from nearly 8 million patients taking potentially hepatotoxic medications.[40] Furthermore, case reports vary in how they eliminate other causes of DILI/liver disease and conduct toxicology testing. One large, multicenter prospective cohort study—the US Acute Liver Failure Study Group—that included 2626 hospitalized patients with acute liver failure or acute liver injury from 1998 to 2015 identified only 41—or 1.6%—that were attributable to dietary supplements.[30] When considered within the context of the number of adults in the United States who report dietary supplement use (58%,[2] which translates

into at least 180 million people), 41 cases across 32 transplant centers over 17 years is very small.

BALANCING THE POTENTIAL HARMS OF DIETARY SUPPLEMENTS FOR PATIENTS WITH CHRONIC LIVER DISEASE

Some might argue that a single death from a dietary supplement is one too many. From the hepatologist's perspective, advising a patient to avoid all dietary supplements may feel like the "safest" approach, if preventing DILI is our singular goal. However, this approach overlooks the potential benefits for the patient and their intention to explore complementary approaches to support their liver health. Furthermore, it fails to recognize the deep cultural roots of many dietary supplements, which are integral to centuries-old traditional practices such as Ayurveda and Traditional Chinese Medicine.[18] This dichotomy—where one party sees benefit and the other party sees harm—sets up a potentially adversarial patient-provider relationship. It discourages open dialogue around the use of that dietary supplement and may lead to a situation in which the patient takes a supplement without all the information or proper monitoring.

There is a more nuanced alternative that considers efficacy and safety to engage in shared decision-making with the patient (Table 3). In this classic risk-benefit framework for evaluating the use of complementary and integrative medical therapies,[41] clinicians are asked to weigh the quality of the evidence supporting efficacy against the weight and seriousness of the documented harms. If there is robust evidence supporting both efficacy for a specific indication and overall safety, then the clinician might encourage a trial of that supplement for that specific indication given the patient's motivation to engage in complementary and alternative medicine and availability (or lack thereof) of conventional therapies. If there is less robust evidence suggesting efficacy but sufficient evidence to support safety, then the clinician might consider accepting the patient's use of this medication with close monitoring for benefit

TABLE 3 General framework for evaluating the use of a dietary supplement in a patient with chronic liver disease (adapted from Weiger et al[41])

	Encourage trial (with monitoring)	Accept (with monitoring)	Discourage
Mechanism of action	Evidence supports a mechanism of action that targets a specific chronic liver disease (eg, viral hepatitis)/symptom/health goal, mechanism of injury (eg, hepatic inflammation and fibrosis), or symptom (eg, pruritus)		No evidence to support a plausibly beneficial mechanism of action
Efficacy	Evidence includes meta-analyses or RCTs Evidence includes multiple cohort studies	Evidence fails to meet criteria for supplements that may be "encouraged"; *or* Evidence is inadequate to conclude whether the supplement is effective or ineffective Evidence fails to meet criteria for discouragement	Evidence includes meta-analyses, RCTs, or multiple cohort studies that demonstrate a *lack of* efficacy
Safety	No obvious theoretical potential for major harm No documented adverse events; *or* Documented adverse events are minor (not life-threatening or permanently disabling)		Documented adverse events are major (life-threatening or permanently disabling); *or* Theoretical potential for major harm Patient-specific concern: minor adverse event that could precipitate hepatic decompensation (eg, grade 1 DILI in a patient with cirrhosis) or violate liver transplant candidacy (eg, alcohol-based extract); drug-drug interactions with liver-specific meds
"Sum" of the evidence	Evidence supports the mechanism of action, efficacy, and safety	Evidence on the mechanism of action and/or efficacy is less robust and/or is inconclusive, but evidence suggests it is safe	Lack of a scientifically plausible beneficial mechanism of action and/or evidence indicates inefficacy or serious risk
Suggested monitoring plan	Start with 12-week trial Monitor for improvement in desired endpoint (eg, liver tests) and/or symptoms		Not applicable
	Monitor blood tests monthly initially, then as indicated for their underlying chronic liver condition	Monitor blood tests monthly initially, then, if the patient responds to the supplement, every 3–6 mo	

Abbreviation: RCT, randomized clinical trial.

(ie, improvement in desired endpoint or symptoms), and for safety (ie, monitoring of liver enzymes). Lastly, clinicians should advise against the use of supplements for which there is sufficient evidence to support *inefficacy* and/or there are documented or potential for serious adverse events associated with that supplement.

Many independent resources exist that offer summaries of the scientific literature on the efficacy, benefits, and potential risks associated with specific dietary supplements for given indications. These include sources such as livertox.nih.gov, www.consumerlab.com, www.naturalmedicines.therapeuticresearch.com, and www.examine.com. In addition, there are independent organizations that will test and certify dietary supplements to ensure the quality of dietary supplements based on standards for purity, potency, and accuracy of labeling (Table 4).[42] In other words, the intent of these quality seals is to indicate that these products do not contain compounds that are not listed on the label, that they contain the dose of the compound that is stated, and that they are manufactured in a way to reduce the risk of contamination. These organizations often offer a seal of certification for supplements that "pass" the testing, which can provide consumers a layer of reassurance regarding supplement quality. In India and China, herbal supplements have been formally integrated into the public health system through government agencies, including the National Medicinal Plants Board (India) and the National Administration of Traditional Chinese Medicine (China), facilitating a structured approach to national oversight of dietary supplements.[43,44] In Europe, dietary supplements are regulated as a type of food by the European Food Safety Authority (EFSA), with additional scrutiny paid to certain substances for which safety concerns have been raised by European Union states (eg, Ephedra species, catechins from green tea extract).[45]

There are a few other important factors to consider when implementing this framework for a dietary supplement for a specific indication in clinical practice. First, what stage of liver disease does the patient have; that is, is the underlying liver condition stable? (eg, autoimmune hepatitis); and does the patient have cirrhosis? These factors may increase the risk profile, as a dietary supplement that is associated with self-

TABLE 4 Examples of certification seals to evaluate the quality of dietary supplements

Label	Comments	Quality seal of certification
Good Manufacturing Practice (GMP)	Enforced by the US FDA A system of regulations, codes, and guidelines for ensuring that manufacturers adhere to strict standards during the production process	
US Pharmacopeia (USP)	An organization that sets quality standards for dietary supplements (in addition to medicines and food ingredients) and offers verification programs to test supplements for purity, potency, performance, and accuracy of labeling	
National Sanitation Foundation (NSF)	Indicates that the product has been independently verified to meet high standards for quality and safety	
Consumerlab.com	Offers a quality certification program to test the purity, quality, and accuracy of labeling Publishes results of testing online	

Abbreviation: FDA, food and drug administration.

limited aminotransferase elevation in the literature may lead to hepatic decompensation in a patient with cirrhosis. Second, what conventional therapies are available for that specific indication—and what is the evidence to support the efficacy and safety of those conventional therapies? Let us say your patient asks for your recommendation regarding a dietary supplement to manage a condition or symptom for which conventional therapies are either nonexistent, ineffective, or intolerable. In this scenario, one might consider *encouraging* a trial of the dietary supplement rather than simply *accepting* it. Third, what is the patient's personal preference for taking the dietary supplement? As conceptualized in the Whole Health model of care, an approach to health care that emphasizes patient-centered care and an alignment of health care with the patient's values,[46] a patient's intention to take the dietary supplement (with or without your formal "recommendation") should be taken into account when discussing the use of a dietary supplement to ensure that an appropriate monitoring plan is in place in the event that you would otherwise have discouraged its use.[47]

PUTTING THE FRAMEWORK INTO PRACTICE THROUGH 3 COMMON CLINICAL SCENARIOS

This is where the art of adapting integrative medicine approaches to hepatology comes in. It requires the synthesis of factors specific to the dietary supplement, the patient, and any conventional therapies that exist for the specific indication or symptom that the patient wishes to manage (Figure 1). Here, we offer a narrative of how this integrative health framework might be applied in 3 common clinical scenarios based on our real-life clinical experience.

Clinical scenario #1: A patient interested in a supplement for which data on the benefits are controversial but for which there is little risk of harm

Case

A 58-year-old woman with MASLD presents to you for an annual follow-up. Her most recent imaging-based noninvasive fibrosis assessment revealed stage 1 fibrosis. She is seeing a dietician regularly and reports that she has increased her weekly cardiovascular exercise. She is frustrated that she is not able to "do more" to help manage her liver condition. After reading about the potential benefits of milk thistle on "liver health" online, she started taking a milk thistle dietary supplement that she purchased at her local drugstore. She reports that she feels that she is "taking action to help her liver" and that her abdominal pain has been better since she started taking it. Her aminotransferases remain stable but mildly elevated.

Pragmatic review of the supplement

Milk thistle *(silybinum marianum)* is a therapeutic herb that contains silymarin, a mixture of flavonoid complexes, of which silybin is the primary active component.[48] In animal models, silymarin has been shown to demonstrate a broad spectrum of hepatoprotective effects, including antioxidant, antifibrotic, anti-inflammatory, and immune-modulatory properties.[49] A search on LiverTox,

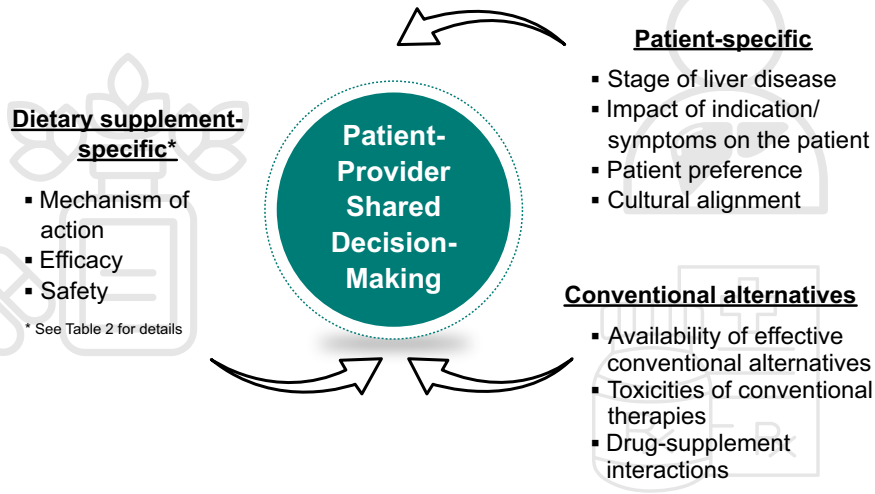

FIGURE 1 Conceptual framework for considering factors specific to the dietary supplement and the patient.

a comprehensive database about DILI supported by the NIDDK and the National Library of Medicine, reveals that milk thistle has a long track record of use in humans without raising substantial concerns about hepatotoxicity related to the compound itself.[50] Studies from before 2010 that included primarily patients with chronic hepatitis B, chronic hepatitis C, or alcohol-associated liver disease supported the safety of milk thistle in humans but no reduction in mortality, biochemical markers of liver inflammation, or liver histology[51]; a well-known randomized clinical trial published in 2012 that included patients with chronic hepatitis C who were interferon treatment nonresponders found no effect of silymarin on serum aminotransferase levels, severely dampening enthusiasm for milk thistle in the management of patients with chronic liver disease (evidence).[52] However, a more contemporary systematic review that included 3846 participants in 29 randomized clinical trials found that silymarin reduced serum liver enzyme levels in the majority of studies.[53] A separate meta-analysis of 26 randomized clinical trials evaluating the efficacy of silymarin in patients with MASLD also demonstrated a benefit of silymarin on serum aminotransferases and hepatic steatosis (among the subgroup of patients with a liver biopsy) (efficacy[.54] Human studies are lacking to support the effect of milk thistle on more clinically robust markers of liver health, including fibrosis progression, hepatic decompensation, or death.

Application to the clinical scenario

In this clinical scenario, the patient is already engaged in the first-line treatment for MASLD and states that she would like to do more. She reports empowerment by taking this supplement and subjective improvement in her abdominal symptoms. While there are no convincing data supporting the benefit of milk thistle on standard MASLD endpoints (ie, fibrosis progression), it may improve liver enzymes, which could help motivate the patient and maintain engagement. The safety profile is favorable.

Shared decision-making

After weighing the (low) risks against the (positive) benefits, you encourage the patient to continue taking milk thistle while emphasizing the importance of nutrition and exercise as the foundational therapy for MASLD. A quick online search of the patient's specific supplement does not reveal any seals of quality assurance (Table 3) for this product, so you discourage the use of this specific supplement. Instead, your research on ConsumerLab.com identifies several independently tested options for milk thistle to recommend, which are also priced within a reasonable range for the patient. She agrees to take one of your recommended options and to monitor her liver enzymes every 6–12 months (aligned with her clinical laboratory test monitoring).

Clinical scenario #2: A patient using a supplement that you research and find it can do harm, so actively discourage use

Case

A 39-year-old man was diagnosed 1 year ago with PSC. His liver enzymes normalized after his episode with acute cholangitis and decompression with endoscopic retrograde cholangiopancreatography. You have previously told him that there are no known Food and Drug Administration-approved therapeutic agents for his condition, to which he has repeatedly expressed dissatisfaction. On this visit, he reports that 3 months ago, he started taking a turmeric supplement after reading about its anti-inflammatory effects online. His liver enzymes remain normal during this visit.

Pragmatic review of the supplement

Turmeric *(curcuma longa)* is a plant in the ginger family that is commonly used as a spice and a medicinal herb in Ayurveda and traditional Chinese medicine. Curcumin is the major active compound that gives turmeric its characteristic marigold yellow. Curcumin is difficult to study because it is unstable and poorly bioavailable, but the compound is believed to exert hepatoprotective effects through its antioxidant and anti-inflammatory properties.[55] There have been several meta-analyses that have demonstrated benefits on some metabolic parameters in patients with MASLD.[56,57] With respect to patients with PSC, the data are scant. One small open-label study including 15 patients with PSC demonstrated that curcumin 750 mg per day was safe during a 12-week period but not associated with a reduction in liver tests or improvement in self-reported health.[58] In addition, a number of case reports have associated supplements containing turmeric with DILI with serum aminotransferase levels often above 1000 U/L, the development of jaundice, and at least 1 fatality.[34,36] Further investigation has linked these instances of turmeric-associated DILI with supplements that were developed to increase the bioavailability of curcumin compound, either with piperine (black pepper) or nanoparticle delivery methods to increase absorption, or to individuals with specific HLA-B*35:01 genetic polymorphism.[24,34] Turmeric has been determined to be a "likely cause of clinically apparent liver injury" by national institutes of health LiverTox.[24]

Application to the clinical scenario

While the anti-inflammatory and antioxidant effects of turmeric could, in theory, benefit patients with PSC, there is little evidence in humans to support its benefit. Furthermore, there is sufficient evidence demonstrating serious risk. Emerging evidence is shedding light on which formulations of turmeric (ie, highly bioavailable curcumin compound vs. whole botanical) and which patients (ie, certain genetic polymorphisms) may be at greatest risk for turmeric-associated DILI, but this evidence is not mature enough to inform clinical decision-making at this time.

Shared decision-making

After the presentation of the high risk-to-benefit ratio to this patient, the patient decides to stop the turmeric supplement. You encourage him, however, to use turmeric as a spice in quantities in everyday cooking.

Clinical scenario #3: A patient with chronic liver disease who is interested in taking a supplement for which there is little evidence of harm, but who also has personal factors that increase his risk for harm

Case

A 48-year-old man with Child-Pugh A cirrhosis secondary to metabolic dysfunction and alcohol-associated steatotic liver disease without clinically significant portal hypertension has persistently elevated liver enzymes despite alcohol abstinence and engagement in the management of his metabolic risk factors. He presents to you with his intention to start *N*-acetyl-cysteine (NAC) and provides you with studies showing benefits in patients with chronic liver disease.

Pragmatic review of the supplement

NAC is a derivative of the amino acid cysteine and serves as a precursor to glutathione, an intracellular antioxidant. While NAC has strong data in support of its benefit in the setting of acute liver injury secondary to acetaminophen overdose,[59] studies evaluating its efficacy in patients with chronic liver conditions are currently inconclusive. However, preclinical models demonstrate that NAC targets intrahepatic lipid accumulation and oxidative stress, offering promise for its potential benefit in patients with steatotic liver diseases.[60] NAC is generally considered safe in humans; National Institutes of Health LiverTox has determined it to be an "unlikely cause of clinically apparent liver injury."[61]

Application to the clinical scenario

In this case, data around NAC itself support potential beneficial mechanisms of action in steatotic liver disease, which this patient has, and its safety even in patients with advanced liver disease. Therefore, the potential harms to this patient present not in the form of the compound itself but in the other forms presented in Table 2 (eg, adulteration, contamination, etc). Such harms may pose a greater risk in this patient due to his underlying cirrhosis.

Shared decision-making

You explore with the patient his motivations to initiate NAC and his understanding of the potential benefits and risks of taking NAC. You discuss with the patient your own pragmatic review of the data around this supplement, including the lack of efficacy for the indication of metabolic dysfunction and alcohol-associated steatotic liver disease. Acknowledging his positive outlook on NAC, balanced with its promising mechanisms of action and its general safety in patients with advanced liver disease, you accept the patient's use of NAC with caution (Table 3) and agree upon a plan to monitor liver function monthly for the first 3 months, then every 3 months thereafter. To reduce the risk of harm, you offer several independently tested options for NAC on Consumerlab.com.

CHALLENGES OF THIS APPROACH AND UNMET NEEDS IN THE FIELD

At first, this process may feel time-consuming and labor-intensive, but, as with any skill in medicine, becomes more intuitive with practice and increased familiarity with the available independent resources. Monitoring for safety, after the initial 12-week trial period, may often overlap with routine monitoring for the underlying chronic liver disease. After performing this process only a few times for each dietary supplement, one can quickly build a personal database of the major dietary supplements that patients with chronic liver diseases seek to take.

This field is in great need of multidisciplinary research to address knowledge gaps in integrating dietary supplements into clinical hepatology practice. First, what is the true incidence of DILI from specific dietary supplements? Standardized capture of dietary supplement use by patients is needed so that robust

pharmacoepidemiologic methods can be applied to calculate true incidence.[62] Second, studies that measure the full range of benefits of dietary supplements including patient-reported outcome metrics—particularly among 9 key symptom targets in patients with advanced liver disease[63]—along with patient engagement are essential to provide a balanced perspective on dietary supplement use in patients with chronic liver disease. Lastly, we believe that the field would benefit from formalized collaboration among multiple disciplines, including hepatology, integrative medicine, Ayurvedic and traditional Chinese medicine practitioners, and medical ethicists to strive for consensus on how to balance the current state of evidence of efficacy and risks, informed consent, and patient autonomy to make decisions about taking dietary supplements.

CONCLUSIONS

Patients with chronic liver disease are increasingly taking dietary supplements to support their liver and overall health beyond conventional therapies and often, without informing or discussing them with their hepatologist. While there are potential risks to the use of dietary supplements, there are also potential benefits. Open discussion between patients and their practitioners about these risks and benefits can facilitate shared decision-making around the use of dietary supplements that can optimize the benefits while minimizing harm through careful selection of supplements (if used at all) and close monitoring for both adverse effects and improvement in desired endpoints. However, these discussions start with practitioners who are open to such discussions with their patients living with chronic liver disease. Practitioners who are considering incorporating supplements into their clinical practice can arm themselves with frameworks, drawn from the discipline of Integrative Medicine, to personalize their recommendations about a specific dietary supplement to their individual patient.

AUTHOR CONTRIBUTIONS

Jennifer C. Lai: study concept and design, and drafting the manuscript. Melinda Ring, Anand Dhruva, and Gloria Y. Yeh: study concept and design, and critical review of the final manuscript.

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CONFLICTS OF INTEREST

Jennifer C. Lai consults and advises Novo Nordisk. She consults for GenFit, advises Boehringer Ingelheim, and received grants from Nestle Nutrition Institute. The remaining authors have no conflicts to report.

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