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REVIEW

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Complementary and alternative medicines and liver disease

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Abstract

Complementary and alternative medicines (CAM) include conventional medical treatments. Patients worldwide use CAM at alarming rates; thus, reports of CAM-related DILI have been on the rise. The clinical presentations include asymptomatic liver test abnormalities, acute hepatitis with or without jaundice, acute cholestatic liver disease (bland or with hepatitis), acute liver failure, severe hepatitis with features of portal hypertension, and acute decompensation of known or unknown cirrhosis that can lead to acute-on-chronic liver failure. Acute hepatitis with or without necrosis, hepatocellular and canalicular cholestasis, herb-induced or CAM-triggered autoimmune hepatitis, granulomatous hepatitis, severe steatohepatitis, and vanishing bile duct syndrome are common liver biopsy findings in CAM-DILI. The presence of preexisting liver disease predicts severe liver injury, risk of progression to liver failure, and decreased transplant-free survival in patients with CAM-DILI. This review discusses global epidemiology and trends in CAM-DILI, clinical presentation, assessment and outcomes, commonly emerging threats in the context of hepatotoxic herbs, pragmatic assessment of "liver beneficial" herbs and health care myths, patient communication, regulatory framework, and future directions on research in CAM.

INTRODUCTION

Complementary and alternative medicines (CAM) encompass products and practices that are not part of standard scientific medical care. Complementary medicine is often used along with standard medical care, both when there is supportive evidence (eg, tai-chi to prevent falls in frail patients) and also when it is lacking (eg, yoga for epilepsy or herbal medicines for HCC).[1,2] Alternative medicine, which is used instead of standard medical therapy, has limited low-quality research attached in support of it (eg, dietary management of cancer instead of pharmacological therapy or homeopathic remedies for the prevention of COVID-19 instead of vaccination).[3,4] Complementary and alternative medical practices include biological therapies (herbs,

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; CAM, complementary and alternative medicines; DILIN, Drug-induced Liver Injury Network; FDA, Food and Drug Administration; HDS, herbal and dietary supplements; HLA, human leukocyte antigen; TCM, traditional Chinese medicine; WHO, World Health Organization.

minerals, and animal parts), mind-body therapies, manipulation-based body therapies, energy healing, and a combination of these. It is important to distinguish between herbal and dietary supplements (HDS) and CAM. The former are considered foods and are defined by the US Food and Drug Administration (FDA) as "products taken by mouth that contain a dietary ingredient intended to supplement the diet." These may include vitamins, minerals, herbs, other botanicals, amino acids, enzymes, organ tissues, and metabolites or their combinations. While CAM therapies are practices that may follow a set of principles based on ancient texts and traditional, cultural, or faith-based components, the use of HDS is largely based on promotions, advertisements, and anecdotes. This review aims to discuss epidemiological trends, clinical assessment, and outcomes of CAM-related DILI from a global perspective, highlight emerging threats with regards to common herbs with hepatotoxic potential, pragmatically discuss myths concerning 'liver beneficial' herbs, and provide insights on patient communication, globally relevant CAM-based regulatory frameworks, and directions for future studies.

GLOBAL EPIDEMIOLOGY

A systematic review of national studies published from 2010 to 2019 revealed that the prevalence of CAM use was very high but possibly underestimated globally. The prevalence of overall CAM use (products and practices) was 24% in Switzerland, 50% in Germany, and 71.3% in South Korea.[5,6] The prevalence of CAM use also varies according to the disease condition, with the highest being 51% among adults with diabetes as well as for various types of cancer.[7,8] The US National Health Interview Survey reported that one-third of patients with a diagnosis of cancer used CAM within the previous 12 months.[9] This may have deleterious effects. A survey of patients from the Commission on Cancer-accredited centers across the United States revealed that patients with treatable cancer diagnoses who opted for CAM therapies instead of the standard of care experienced significantly higher death rates than those who did not.[10]

Trends in CAM use among patients with the liver disease vary in the context of the region as well as the etiology of liver disease globally. Two decades ago, the prevalence of CAM use among patients with liver disease in the United States was 39%, and the variables found to be predictive of alternative therapy use included female gender, young age, education, income, and geography.[11] A 2017 study, where 41% of patients with liver disease reported using CAM in the prior year predominantly did so to treat symptoms (anxiety or depression and fatigue) rather than their underlying liver disease and most commonly used herbal supplements.[12] A Turkish study revealed that more than a quarter of patients with chronic viral hepatitis used CAM, whereas a Canadian study showed that close to 71% of patients diagnosed with chronic viral hepatitis B infection used complementary therapies and alternative medicines.[13,14] A study in the United States showed that nearly 42% of patients used CAM after the diagnosis of autoimmune hepatitis, while another study demonstrated that CAM therapy use was prevalent in more than one-fourth of patients with a diagnosis of any-cause chronic liver disease, which commonly included dietary supplements, herbal products, and homeopathic remedies.[15,16] Nonetheless, a survey of liver disease patients attending a tertiary care center in Saudi Arabia revealed that more than half reportedly used CAM, and a significant proportion of CAM users had a strong family history of CAM-related health-seeking behavior.[17] In an Indian context, we showed that 68% of persons with cirrhosis used CAM.[18] The use of CAM among patients in general is alarmingly high across the globe, with an increasing trend driven by various political[19] and socio-economic factors, health care system approachability, chronicity, and natural history of disease,[20] as well as physician-patient communication and health literacy.[21,22]

REGULATIONS

In the United States, the National Center for Complementary and Alternative Medicine (NCCAM), a center within the National Institutes of Health, is concerned with the practice of CAM and provides 'evidence-based' public discourse on various supplements, medicines, and practices. The FDA, under the Federal Food, Drug, and Cosmetic Act/Public Health Service Act, regulates CAM products and practices but does not approve them. The FDA regulates CAM as a biological product, cosmetic, drug, device, or food in the context of good manufacturing practices and ethical sales. Only when a CAM product(s) or practice has been found to harm the public does the FDA control and regulate further dissemination of that product(s). For example, if a person or company decides to produce, promote, and sell a raw juice product for general wellness as a food supplement, the FDA would only regulate it for good manufacturing practices. However, if the product was marketed with the intention to use it as part of a specific disease-related treatment, then the FDA subjects it to regulations as a drug under the Federal Food, Drug, and Cosmetic Act. Thus, most CAM products and practices remain unregulated from a disease and preventive claims perspective because they thrive on promotions of general wellness, marketed on 'vague science-sounding jargon that excludes stringent scrutiny.[24–26]

In the European Union, the European Food Safety Authority provides independent scientific advice and communicates the existing and emerging risks associated with the components within the food chain. In Europe, herbal products are mostly classified as food or health supplements and marketed. Nonetheless, an herb may be considered a medicinal product when it is described as having properties for treating or preventing diseases in humans and must undergo stringent studies to showcase its efficacy and safety as prescribed for standard medicines. Only a few countries have general CAM legislation, some have specific CAM laws, and others have included CAM in their general health care laws. Some regulate only specific CAM treatments, while most CAM products are subjected to the same market authorization procedures as conventional medicine, apart from documentation of efficacy.[27–29]

In the Asian context, such as China and India, and even in more technologically advanced nations, such as Korea and Singapore, CAM products such as traditional medicines are officially recognized and integrated into the public health care system. In these regions, regulation of CAM becomes secondary, and promotion of traditional medicines and practices is prioritized, bypassing scientific evidence driven by nationalism, to maintain cultural, political, faith, and religion-based sentiments alive within the public.[30,31] This has resulted in an increased relative prevalence of CAM-DILI (among all DILI) from traditional medicines and dietary supplements within the Asian continent, especially within countries that normalize integrative medicine, with 17.1% in Japan, 18.6% in China, 71% in Singapore, and 72.7% in Korea.[32]

PHARMACOVIGILENCE NETWORKS

At a global level, as well as at the national level, public pharmacovigilance systems help capture adverse events related to CAM therapies. These systems are additionally strengthened by investigator-initiated, medical-society-endorsed DILI networks within the public health system, which help in the prompt identification of adverse events due to drugs, herbs, or supplements. The US Drug-induced Liver Injury Network (US-DILIN) and similar networks in Spain (Spanish-DILIN), Latin America (Latin American-DILIN), and the recently formed Indian-DILIN are examples of investigator-initiated, medical-society-endorsed DILI networks.[33,34] At the global level, the Uppsala Monitoring Centre, a self-funded, mission-driven, nonprofit foundation, works with the World Health Organization (WHO) and maintains the VigiBase, the driving force behind the WHO Programme for International Drug Monitoring. VigiBase is the largest database of its kind in the world, with over 30 million reports of suspected adverse effects of medicines, submitted since 1968, by member countries of the WHO Programme for International Drug Monitoring, continuously updated with incoming reports.[35] In the United States, the FDA receives industry-reports, institute-reports, hospital-reports, or individual-reports of adverse drug reactions, which undergo further scrutiny and vetting.[36] In the European Union, the EudraVigilance, launched by the European Medicines Agency maintains a database of reported side effects due to drugs and supplements.[37] The Netherlands Pharmacovigilance Center Lareb is specialized in promoting the reporting of adverse drug reactions through causality assessment and signal detection and performs cohort event monitoring and communication. The Lareb collates adverse drug reaction data from the European Medicines Agency and WHO-VigiBase.[38] The Australian Government's Therapeutic Goods Administration, functioning under the Department of Health and Aged Care, captures pharmacovigilance data related to medicines and unapproved therapeutic goods, including CAM.[39] From an Asian perspective, even though pharmacovigilance systems exist for prescription drugs, well-developed databases for monitoring, capturing, and communicating adverse drug reactions from CAM therapies have not fully evolved. In India, the Central Drugs Standard Control Organization maintains the PvPI or the Pharmacovigilance Programme of India for prescription drugs, while the Ayush Suraksha consisting of national, intermediary, and peripheral pharmacovigilance centers run by the Ministry of Ayush supposedly maintains a database of side effects due to Ayurveda, Homeopathy, Unani and Siddha practice related therapies.[40,41] The All India Institute of Ayurveda, New Delhi, is the National Pharmacovigilance Coordination Centre for the implementation of Ayush Suraksha, which is yet to report any side effects from CAM therapies. In China, the pharmacovigilance of TCM is still largely dependent on the published literature review of publicly available data maintained by the China National Medical Products Administration.[42] These regulatory bodies inform their respective public of potentially unsafe medicines and medical products when a significant minimum number of adverse reactions are captured in their databases. However, our understanding of DILI, including CAM-DILI, has been largely dependent on peer-reviewed publications from single or multicenter hospital-based studies and large, regional investigator-initiated, medical-society-endorsed DILI networks.

According to 4 large prospective studies (India, Spain, the USA, and Iceland) on DILI, CAM was the second most common cause of DILI, after antimicrobial use.[43] CAM-DILI has male predominance in the Indian context, while more women were found to be affected in published series from the West and other southeast Asian regions.[44,45] Liver injury due to CAM in the West is predominantly caused by the use of HDS for weight loss.[24] CAM-DILI is not commonly reported in Europe,

but its relative prevalence compared with that of conventional DILI is less than that in Latin America. India is the only country on the Asian continent where CAM-DILI is not the most common cause of liver injury, predominantly because anti-tuberculosis therapy and its impact on the liver remain relevant in this developing nation.[46] In Asian countries, CAM-DILI commonly occurs with the use of traditional medicines, medicinal plants, and folk remedies. For example, traditional Chinese medicine (TCM) accounts for most liver injuries caused by CAM in China, Korea, Singapore, and Japan. Thus, the implicated agents for CAM-DILI in Asian studies are nearly all traditional medicines or crude herbs, whereas in the West, it is mostly HDS, which includes anabolic steroids and multi-ingredient nutritional supplements. Similarly, contrary to publications on DILI from other parts of the world, the largest study on DILI from mainland China demonstrated that CAM, mostly TCM, and crude herbs were the leading causes of liver injury in almost 27% of the cases.[47] In the majority of published series from across the world, CAM-DILI was most commonly of the acute hepatocellular type with a higher rate of hospitalization, severity of liver injury, liver test abnormalities, increased risk of mortality, and need for liver transplantation compared to non-CAM-DILI.[43,46,48]

CLINICAL PRESENTATION, ASSESSMENT AND OUTCOMES

Presentations

The clinical presentation of DILI due to CAM products is usually nonspecific and can mimic every other acute or chronic form of liver disease. Patients can present with asymptomatic liver test abnormalities, symptomatic (nausea, loss of appetite, fever, musculoskeletal complaints, and skin rash) acute hepatitis with or without jaundice, acute cholestatic liver disease (bland or with hepatitis), acute liver failure (ALF), severe hepatitis with portal hypertension features (most commonly ascites), or acute decompensation (of known or unknown) cirrhosis, which may progress to acute-on-chronic liver failure (ACLF).[49] Rare presentations include vascular liver injury in the form of symptomatic or asymptomatic acute PVT, and hepatic veno-occlusive disease. From a histological perspective, acute hepatitis with or without varying degrees of necrosis, hepatocellular and canalicular cholestasis, herb-induced/triggered autoimmune hepatitis, granulomatous hepatitis, severe fatty liver disease, non-cirrhotic portal hypertension, (drug-induced) alcohol-associated liver disease, and vanishing bile duct syndrome have been described with CAM use. Liver injury can occur within several days to up to 3 months after the initiation of a new herbal supplement or product.[45,49] CAM-DILI is predominantly idiosyncratic in nature, and some herbs and herbal products have been reported to cause liver injury after many months or years. A classic example is the herbal laxative Indian Senna (Senna Alexandrina or *Cassia angustifolia*), which causes cholestatic liver injury after months or years of use.[50] Apart from hepatic involvement, CAM-related formulations can also present toxicity related to heavy metal poisoning, notably with lead, arsenic, or mercury.[51] Extrahepatic manifestations, such as skin, central nervous system, renal system involvement, and bone marrow failure, have also been reported.[52–54]

A thorough and accurate clinical history of exposure to CAM, onset of symptoms, course of illness, liver test abnormalities, and peak abnormalities are pertinent for the diagnosis of CAM-DILI. Furthermore, clinical and biochemical improvements with de-challenge (removal of offending CAM) are valuable in confirming hepatotoxicity. Most cases resolve spontaneously; however, some CAM-liver injuries can progress to chronic liver injury, ALF, or ACLF, with a high rate of mortality in the absence of a timely liver transplant.[55,56]

Assessments

Patients with suspected CAM-DILI should be thoroughly assessed, which involves a full history of drug use, assessment of the pattern of liver injury based on serum biochemical tests, and ruling out other competing causes of liver disease. Knowledge of probable drug-related adverse effects on the liver, as well as a high level of awareness of DILI, improve the accuracy of history taking.[57] Three patterns of CAM-DILI, based on baseline serum alanine transaminase and alkaline phosphatase ratios from the first investigations, can help in categorizing the injury as hepatocellular, cholestatic, or mixed. This is called the *R*-ratio, which is a reliable tool that helps correlate biochemical and pathological injury patterns. The *R*-value is defined as serum alanine transaminase/upper limit of normal divided by serum alkaline phosphatase/upper limit of normal. An *R*-ratio of $\geq$ 5 implies hepatocellular injury, $\leq$ 2 cholestatic injuries, and $2 < R < 5$ mixed injuries.[58] An important tool in diagnosing CAM-DILI is causality assessment, which is a systematic evaluation of the strength of the relationship between CAM(s) exposure and adverse event(s). Over the years, multiple assessment methods have been used, such as the Roussel Uclaf Causality Assessment Method (RUCAM) Clinical Diagnostic Scale, Japanese criteria, and structured expert opinion processes, such as the US-DILIN consensus. Each method has its own advantages and disadvantages. For example, the structured expert opinion process produced higher likelihood scores than the Roussel Uclaf Causality Assessment Method, but it has not been externally validated and is therefore not widely applicable.[59] Nonetheless, the recently devised

revised electronic version of the (RECAM) designed for acute idiosyncratic liver injury, is a promising evidence-based update. Nonetheless, RECAM was built using DILI cases due to prescription medications and not herbal or dietary supplements; thus, for suspected CAM-DILI, it must be used with caution.[60] Physicians caring for patients with suspected CAM-DILI must keep in mind the utility of these tools but must also realize that these are not substitutes for good clinical judgment because the heterogeneity of CAM-DILI and individual patient idiosyncrasies does not allow for a "one size fits all" approach towards diagnosis (Figure 1). Abdominal ultrasonography should be performed routinely in all patients, while advanced imaging may be reserved for those with high clinical suspicion of competing causes. Although liver biopsy may be considered only if an alternative diagnosis needs to be ruled out, it may also be performed when patients fail to respond to conservative care after the withdrawal of the offending CAM.[61]

Published studies on CAM-DILI and related liver histology are mostly from Asia. Liver biopsy features include macrovesicular and microvesicular steatosis, cholestasis, hepatocyte apoptosis, epithelioid granulomas, and eosinophilic, neutrophilic, and lymphoplasmacytic infiltration. Inflammation, necrosis, and Ishak fibrosis scores were higher in patients with cholestatic and mixed-type liver injury than in those with predominantly hepatocellular injury. Common liver biopsy findings in most CAM-DILI include interface hepatitis, eosinophilic inflammation, hepatocellular/canalicular cholestasis, and a higher severity and extent of hepatocellular necrosis. Portal-based inflammation and siderosis are more common than lobular and ductular reactions.[45,61]

In the context of Ayurveda-CAM-DILI, liver biopsy features can help with prognostication, as severe grades of hepatic necrosis (confluent, submassive, and massive types) at presentation were associated with lower transplant-free survival.[43] Even though acute hepatitis is the most common pattern observed on liver biopsy, a wide range of findings mimicking other acute liver injury conditions (autoimmune, steatohepatitis, vascular injury, and chronic hepatitis) are identifiable or co-exist, making the diagnosis of CAM-DILI histologically challenging.[45,51,61] Nonetheless, the predominance of eosinophilic or granulomatous inflammation, well-defined perivenular necrosis, and severe cholestatic features generally favor a diagnosis of CAM-DILI (Figure 2).[62]

Additional assessments—review of CAM products

A case-by-case review of the products implicated in CAM-DILI is important to address the four main concerns.[63] One is to confirm whether the product contains a single or multi-herbal ingredient. Second, to identify known and well-documented hepatotoxic components. Third, in the case of unlabelled products, AQ6 where possible, to subject the same for chemical, toxicological, and barcoding-based herbal component identification whenever possible to improve the suspected diagnosis of CAM-DILI. Finally, to identify adulterants and contaminants that could have contributed to the hepatotoxicity of the formulation. In most cases, patients with CAM-DILI used multiple multiherbal formulations, which would not always be available for retrieval and scrutiny. Nonetheless, retrieval and analysis of the implicated CAM(s) are not mandatory for the diagnosis of DILI, which remains a clinical diagnosis through structured causality or expert consensus using diagnostic exclusions and temporal correlation driven by strong clinical suspicion.

Quality concerns of CAM products have been a matter of discussion throughout the decades, as manufacturing practices within the alternative medicine industry lie in the eye of the storm about poor standards, adulteration, and contamination. In a study conducted in Singapore, herbal medicines were found to be adulterated with phenylbutazone and caffeine.[64] A study from India demonstrating CAM-DILI due to Ayurvedic herbs revealed that when herbal supplements were subjected to chemical analysis and toxicology, and compared to commonly prescribed standard prescription drugs, the latter had zero instances of contamination or adulteration.[51] In the former, unacceptably high levels of toxic metals and hepatotoxic volatile compounds were observed. Another Indian study examined CAM products consumed by patients with severe alcohol-associated liver diseases. It found adulterants such as antibiotics, chemotherapy agents, nonsteroidal anti-inflammatory drugs, alcohol, antidepressants, anxiolytics, recreational drugs, and heavy metals up to 100,000 times above the detectable range.[65] Across the globe, a growing body of evidence demonstrates that CAM suffers from manufacturing flaws and misuse of synthetic drugs to improve efficacy at the cost of patient safety.[66] Reports from Taiwan have suggested that 24% of all samples were contaminated with at least 1 standard pharmacological agent.[67] Similarly, heavy metal contamination of CAM and associated poisoning at the individual and community levels have been described with Ayurvedic products. A report from India on outcomes related to "Ayush-related immune boosting" practices among patients with cirrhosis during the COVID-19 pandemic revealed that retrieved Ayurvedic, Homeopathic, and other CAM formulations contained detectable levels of arsenic (40%), lead (60%), and mercury (60%), along with a host of other plant-derived hepatotoxic compounds, toxic industrial solvents, and alcohol.[68] The use of Ayurvedic and Homeopathic products with alcohol and heavy metal contamination and adulteration, resulting in severe morbidity and loss of life, has continually been reported in the medical

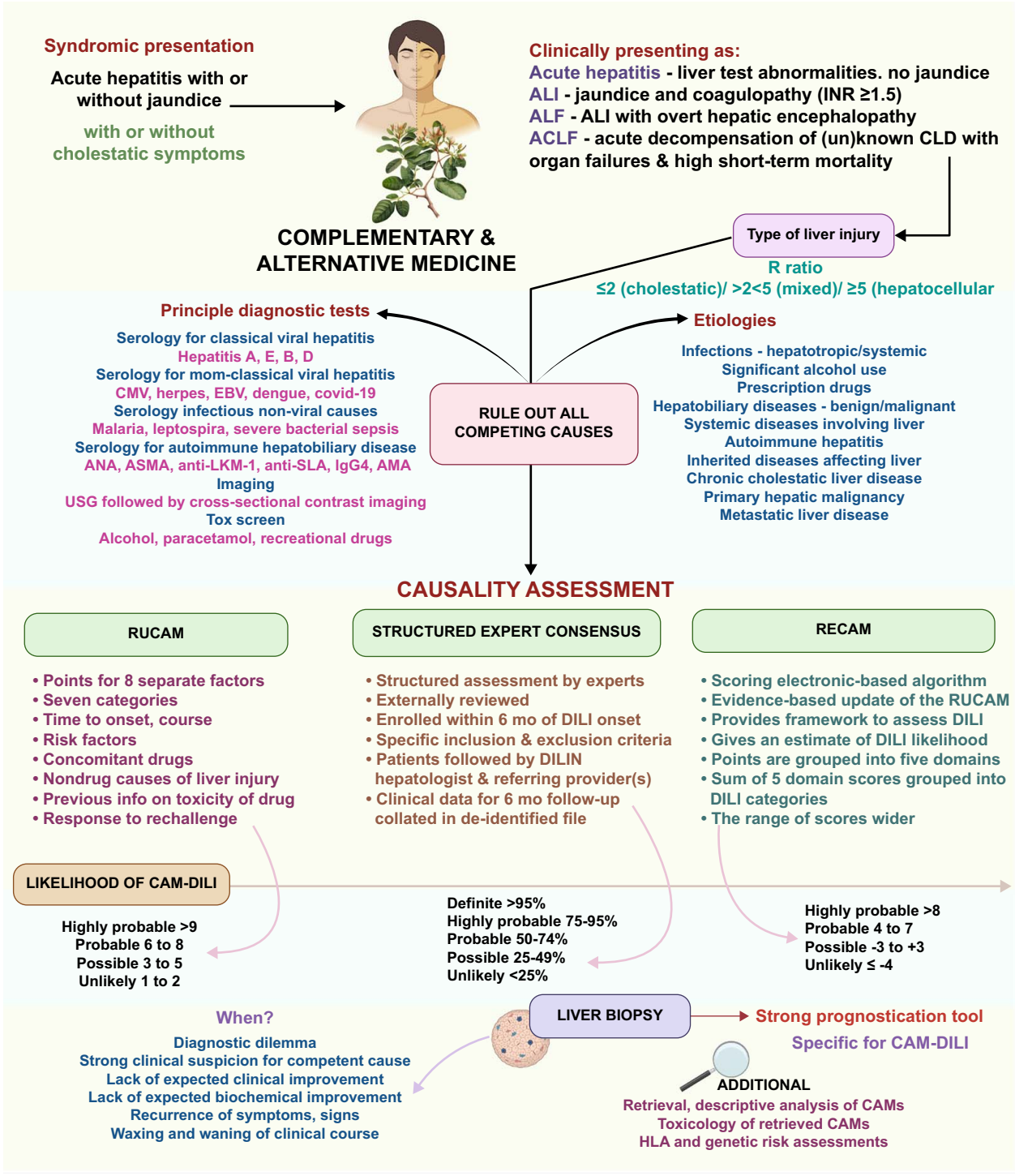

FIGURE 1 Approach and assessment algorithm for the diagnosis of complementary and alternative medicine (CAM)-related DILI. Abbreviations: ALI, acute liver injury; ALF, acute liver failure; ACLF, acute-on-chronic liver failure; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; anti-LKM-1, anti liver-kidney-microsomal antibody; anti-SLA, antibody to soluble liver antigen; AMA, anti-mitochondrial antibody; USG, ultrasound imaging; RUCAM, Roussel Uclaf Causality Assessment Method; RECAM, revised electronic version of RUCAM, HLA, human leukocyte antigen.

literature. Theruvath et al published the first large series of homeopathic remedies related to CAM-DILI and analyzed multiple formulations retrieved from patients. Even in "supposed" ultra-dilute Homeopathic formulations, toxicology discovered large quantities of ethanol, hazardous solvents, corticosteroids, antibiotics, sedatives, synthetic opioids, heavy metals, and toxic phytocompounds.[69]

In recent times, the US FDA and Australian Department of Health have issued multiple warnings

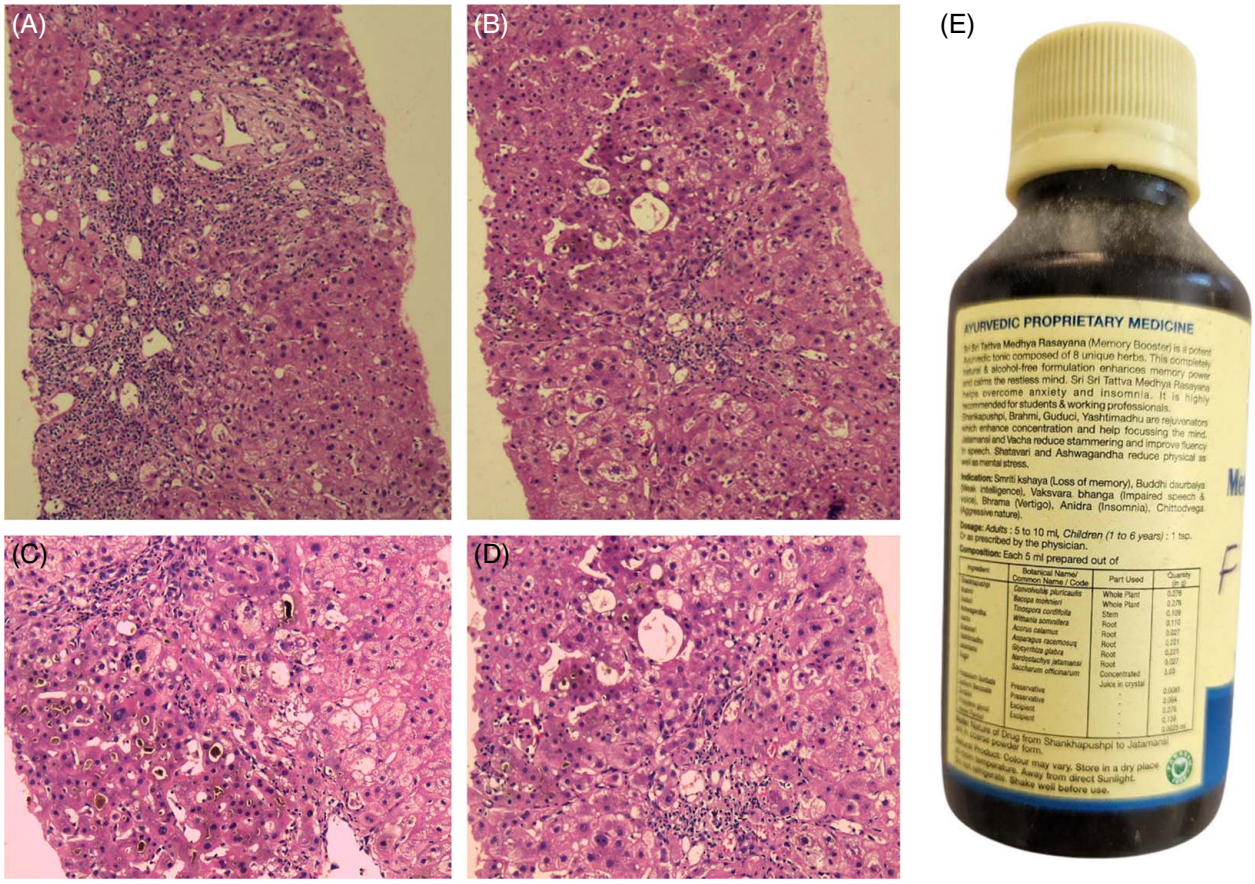

FIGURE 2 Classical example of Ayurvedic multiherbal product-induced liver injury. Liver biopsy reveals extensive neutrophilic and eosinophilic portal inflammation (A, hematoxylin & eosin stain, ×20), interface hepatitis and lobular inflammation (B, hematoxylin & eosin stain, ×20), severe hepatocellular and canalicular cholestasis with feathery degeneration (C, hematoxylin & eosin stain ×40) along with perivenular necrosis (D, hematoxylin & eosin stain, ×40). The implicated Ayurvedic product is shown in E, which was consumed for 28 days for improving memory and general wellness. It contained known hepatotoxic herbs—ashwagandha and giloy.

on contaminated and adulterated Ayurvedic products containing ingredients such as *Azadirachta indica* (Neem), *Acorus calamus* (Vacha or sweet flag), and various heavy metals that pose a threat to health and life.[70,71] The knowledge that the CAM industry and its products remain unregulated and, hence, consumers could experience a high risk of adverse events and organ injury remains an open secret that persistently and consistently escapes scrutiny, review, and reform. However, physicians, the public, and the patient population need to understand the avoidable disease burden consequences that stem from misinformation-related health-seeking behavior and strive to reduce exposure to potentially dangerous CAM products and practices.[72]

Outcomes

Earlier reports from South Asian countries have demonstrated high mortality rates associated with TCM-related DILI. A series from Singapore showed that TCM was the most common group of drugs implicated in 52% of patients with DILI, with a mortality rate of close to 10%.[73] An older Japanese study showed that symptoms, such as general malaise, nausea, and anorexia, were more frequent in the CAM group than in the prescription medicine-related DILI group.[74] A prospective nationwide study from Korea demonstrated that the severity of liver enzyme abnormalities was greater in those with CAM-DILI, and all patients who died or required liver transplantation belonged to the CAM group.[75] In the largest study on DILI from Mainland China, the trends for hepatoxicity were alarmingly high for TCM, with ~5% death rate in those severely affected.[47] A 2015 Chinese study revealed that more than one-third of patients developed DILI due to TCM, with an overall mortality rate of 9%, which included 70% dying due to progressive liver failure.[76] The Model for End-Stage Liver disease score and hypoalbuminemia was an independent predictor of death. Similarly, a recent systematic review from China revealed that TCM was the most common cause of DILI, and a higher risk of death and need for liver transplantation was notable in patients with cholestatic liver injury, with a mortality rate of ~5%. Male sex, high

direct bilirubin, and aspartate aminotransferase levels, and low serum albumin levels were predictors of mortality.[77]

In the Indian context, an earlier study showed that traditional medicine-related ALF was a strong predictor of death, while another study from India showed that even though the contribution of Ayurvedic herbals to DILI was small, death due to progressive liver failure was quite high (~50%).[78,79] In a study by Philips et al on acute liver injury due to the use of Ayurvedic formulations, the overall mortality rate was 19%. The independent predictors of death included the presence of arsenic and mercury in the herbal formulations and the presence of HE and hypoalbuminemia at presentation.[51] A study on the use of CAM in patients with cirrhosis showed that 36% developed severe CAM-DILI leading to ACLF, of which 53% died without liver transplantation, with a median survival of 194 days. In this study, the presence of HE at presentation, the Chronic Liver Failure Consortium score, total bilirubin, presence of hyponatremia, and high leukocytosis along with higher grades of ACLF predicted short (1–3 mo) and long-term (6–12 mo) mortality.[18] An Indian study showed that patients with severe alcohol-associated hepatitis who opted for Ayurvedic treatments at the outset developed severe CAM-DILI over severe alcohol-associated liver disease, resulting in 6-month survival of only 18% compared with 52% of those who were treated initially with standard medical care. Liver histology revealed varying grades of severe necrosis, severe hepatocellular and canalicular cholestasis with predominant lymphocytic-portal-inflammation, and interface hepatitis among patients with CAM-DILI, and the presence of necrosis predicted a higher risk of death.[65] Hepatic necrosis and portal-based neutrophilic inflammation were predominant in CAM-DILI due to Ayurvedic multiherbal products and necrosis, portal and lobular neutrophilic inflammation, and eosinophilic infiltration with cholestasis in homeopathic-remedies related DILI.[68,69] A study on Ayush-related “immune boosting” leading to liver injury,[68] as well as a series of homeopathic-remedies–related DILI[69] demonstrated that CAM products sold as wellness supplements could potentially cause worsening of preexisting liver disease or result in severe liver injury with progression to liver failure, resulting in a mortality rate as high as 45%.

The APASL study on ACLF due to DILI found that the most common acute cause of liver injury was traditional medicine and that chronic liver disease was secondary to alcohol use. The authors found that encephalopathy, bilirubin, blood urea, lactate, and the international normalized ratio predicted mortality.[80] The presence of preexisting liver disease was an independent predictor of severe liver injury, progression to liver failure, and lower transplant-free survival in patients with CAM-DILI. Overall, published evidence shows that even though CAM-DILI was higher among the Chinese population and from southeast Asian regions, the mortality was worse in patients with CAM-DILI on the Indian subcontinent.

EMERGING THREATS

There are 3 primary ways in which information about DILI linked to CAM has been gathered: case reports, case series, and descriptions provided by large retrospective or prospective studies performed at hospitals, institutes, or regional and nationwide databases. Published evidence has shown that specific CAM products or herbs are implicated in hepatotoxicity in the context of the region of origin of such studies. For example, in the context of TCM, the herbs commonly implicated in hepatotoxicity include Fu Ling (*Sclerotium poriae cocos*), Huang Qin (*Radix scutellaria baicalensis*), Gan Cao (*Radix glycyrrhizae*), Ze Xie (*Alisma orientalis*), Chuan Xiong (*Rhizoma ligustici*), *Polygonum multiflorum* (He Shou Wu), *Ephedrae Herba*, *Scutellariae Radix* (skullcap), *Radix polygoni multiflora*, *Panax pseudo-ginseng*, *Tripterygium wilfordii*, saffron, and shenbao mixture.[81] Nonetheless, hepatotoxicity related to the use of these herbs is mostly endemic to China and Southeast Asian countries and seldom reported in other Asian regions or the West. A detailed review of the toxicity profiles and published reports of TCM-DILI is beyond the scope of this paper and is exhaustively reviewed elsewhere.[77,82] In the current era, where social media influences health-seeking behavior, specific herbs associated with traditional medicine and CAM practices are important in the context of emerging reports related to hepatotoxicity that require pertinent discussion.

Curcuma longa (Turmeric)

Curcuma longa is the most well-known and cultivated plant belonging to ~120 species in the *Curcuma* genus of the ginger family. The rhizome is the most widely utilized portion of this plant and includes a wide range of bioactive chemicals, such as nonvolatile curcuminoids and its derivatives bisdemethoxy curcumin and dimethoxy curcumin, as well as volatile oils, such as monoterpenoids and sesquiterpenoids.[83] Whole turmeric, in powders, tablets, or decoctions, or its most bioactive ingredient curcumin, in highly bioavailable forms, are used in traditional Ayurvedic remedies or as dietary supplements, respectively.[84] Turmeric has a bioavailability of less than 1%, resulting in low circulating quantities for effective systemic activity. Turmeric contains up to 5% curcumin, which means that it only contains 5% of the bioactive component, and only 1% of that 5% is accessible for action in the body when turmeric is consumed. This amount is insignificant for

turmeric to exhibit any biological activity in humans.[85] Curcumin, a bioactive molecule, is a PAIN or pan-assay interference compound. In assay trials, PAIN chemicals exhibited many forms of activity, which were incorrectly ascribed to the activity of the drug studied. These bioactivities are caused by misleading processes that occur across other chemical components in the experiment rather than by interactions with cells or tissues.[86] Furthermore, turmeric and its bioactive ingredient, curcumin, are also classified as IMPs, or "invalid metabolic panaceas." invalid metabolic panaceas are chemicals that offer false promises in early trials but have little or no impact in a controlled context, such as in clinical research.[87] This is supported by the fact that turmeric and curcumin are ineffective "lead compounds." A good lead compound has high potency (strength to cause an effect) at low concentrations; a confirmed, selective, and traceable mechanism of action; adequate chemical stability and bioavailability; and stable and meaningfully flexible absorption, distribution, metabolism, excretion, and toxicological properties, all of which are turmeric lacking.[88] Concentrated and highly bioavailable forms of turmeric and curcumin are now commercially available. Because of these formulations, there has been an upsurge in published cases of turmeric-based liver damage. Two important investigations have highlighted the hepatotoxicity of turmeric supplements, triggering regulatory responses from several health care authorities. An examination of the Italian Phytovigilance database and a systematic evaluation of case reports found 7 occurrences of acute hepatitis in Tuscany, where hepatotoxicity was linked to *Curcuma longa* formulations.[89] As a result, the Italian government banned all turmeric-related health claims and issued warning labels for turmeric-based dietary supplements.[90] Similarly, US-DILIN reported a rising problem of liver damage associated with turmeric formulations.[91] They identified 10 cases of turmeric-related liver damage, the majority of which occurred in 8 women with a median age of 56 years. Histopathology demonstrated acute hepatitis or mixed cholestatic hepatic damage with eosinophils, and liver injury was primarily hepatocellular. Five patients were admitted to the hospital, and 1 patient died of severe liver failure. The presence of turmeric was confirmed by chemical analysis in all the formulations examined, and 3 of them also included piperine (black pepper). Human leukocyte antigen (HLA)typing revealed that 7 patients had HLA-B*35:01, which is considered a risk factor for idiosyncratic liver injury from turmeric supplements.[92] The Australian Government's Department of Health and Aged Care, Therapeutic Goods Administration, recently issued a warning to the public about the risk of liver damage from turmeric-based dietary supplements.[93] In conclusion (Table 1), while the rise in liver harm from highly bioavailable forms (nano-formulations or combined with piperine) of turmeric supplements is on the rise as a result of intensive advertising of its therapeutic advantages exaggerated by weak preclinical research. People homozygous for *HLA-B*35:*01 allele are susceptible, and liver injury is generally hepatocellular in nature but self-limiting, although in rare cases, it may lead to ALF.

Tinospora cordifolia (Giloy, Guduchi)

The common English name for *Tinospora cordifolia*, which is Giloy (Hindi) or Guduchi (Sanskrit), is heart-leaved moonseed. Since ancient times, this herb has been incorporated into a multitude of proprietary and traditional herbal formulations within the practices of Ayurveda and Siddha (South Indian CAM). Folk medicine employs the roots, stems, and leaves of Giloy to treat a variety of disorders despite the lack of conclusive evidence of their clinically significant therapeutic benefits.[94] Phytocompounds found in plants are known for their high bioactivities. Despite preclinical investigations in cells, tissues, and small animals demonstrating various cellular bioactivities, rigorous trials have yet to confirm any clinically significant benefits in humans.[94] At present, Giloy is the most frequently reported etiological agent of CAM-DILI in the Indian subcontinent. Six patients were initially diagnosed by clinicians in Mumbai with acute hepatitis directly related to Giloy herb ingestion.[95] The authors reported that the immune stimulant mechanism of the herb induced an autoimmune-like hepatitis/unmasked subclinical autoimmune chronic liver disease, resulting in severe liver toxicity when consumed. Additionally, in their nationwide multicenter investigation, the Liver Research Club India members published the most extensive series of giloy-induced liver injuries.[96] A total of 43 patients were documented, with over half being female, who presented with ALF, acute hepatitis, or acute exacerbation of chronic liver disease after ingesting Giloy. Giloy was associated with autoimmune-like hepatitis, and the herb may have the ability to reveal autoimmune hepatitis in individuals with silent autoimmune hepatitis-related preexisting liver disease, according to the findings of the study. Consistent reports of CAM-DILI associated with Giloy have been received from various regions worldwide, with the Indian subcontinent being the primary area.[97–101] Liver biopsies frequently reveal lymphoplasmacytic lobular inflammation, interface hepatitis, hepatocyte rosettes, hepatocellular and canalicular cholestasis, and portal or lobular neutrophilic and eosinophilic infiltration. The cis-clerodane-type furano-diterpenoids present in *Tinospora cordifolia* can induce hepatotoxicity. Extensive documentation exists regarding the immunostimulatory properties of Giloy associated with autoimmune hepatitis.[96] Giloy-CAM-DILI rarely results in fatalities, and patients respond favorably to conservative

TABLE 1 Pertinent studies on Curcuma longa (Turmeric [or its bioactive compound curcumin])-related liver injury

No.	Author/year/patients	Liver injury and associated features	Clinical outcomes and comments
1	Lukefahr et al/2018/N = 1	Elderly woman Underlying metabolic syndrome, Raynaud's syndrome, irritable bowel syndrome Turmeric supplement intake for 8 months Autoantibody (p-ANCA) was positive Biopsy showed neutrophils, lymphocytes, and plasma cells-based moderate to marked portal inflammation with focal piecemeal portal necrosis Subsequent reassessment of the liver biopsy by the authors revealed autofluorescent inclusions in the pigment-laden histiocytes with an excitation/emission spectrum consistent with curcumin, a turmeric-derived polyphenol or possibly lipofuscin	Abnormal liver tests significantly decreased within 30 d of discontinuation of turmeric supplement, which normalized by 13 mo and have remained normal even after 3 years of follow-up
2	Luber et al/2019/N = 2	One male and 1 female One patient had re-challenge, and liver injury recurred None had significant comorbidities Liver biopsy (done in 1 patient) showed florid inflammatory cell infiltrate comprising lymphocytes, histiocytes, neutrophils, scattered eosinophils, and minimal plasma cells in the portal tracts with interface hepatitis The turmeric supplement tested negative for drugs, adulterants, or toxic heavy metals	Both patients survived Liver injury resolved after withdrawal of offending herbal supplement Complete resolution of hepatitis in 1 mo No recurrence of hepatitis was noted on follow-up
3	Imam et al/2019/N = 1	Elderly female No significant comorbidities One month use of curcumin-only supplement (500 mg) Hepatocellular type of liver injury No liver biopsy was performed	Complete resolution of hepatitis in 42 d No re-challenge was performed No recurrence of hepatitis on follow-up
4	Gasbarrini et al/2019/N = 4	Four patients, aged 25–45 y, 3 females and 1 male Hypertransaminasemia up to 3–6 times with respect to normal value, and increasing of gamma-glutamyl transpeptidase up to 4–8 times the norm was found	Only one of 4 cases had coagulation failure Hepatocyte necrosis and cholestasis regressed after the spice withdrawal Only in 1 case hepatitis lasted for 20 d
5	Abdallah et al/2020/N = 1	A 51-year-old woman Daily use 500 mg of turmeric DS capsules (each capsule containing: 400 mg of turmeric powder, 50 mg of turmeric extract, and 50 mg of organic ginger powder) for 45 d Hepatitis associated with myalgias and fatigue Liver biopsy demonstrated moderate mixed inflammation consisting of neutrophils, eosinophils, and lymphocytes involving the portal areas	Abnormal liver tests reduced by 50% in 6 days and complete resolution of hepatitis in 8 weeks No recurrence of hepatitis noted during the follow-up period
6	Chand et al/2020/N = 1	A 62-year-old woman Treated breast cancer and in remission Turmeric tablets for 10 mo for "wellness" Hepatitis was associated with myalgias, fatigue, and a widespread urticarial rash on her limbs and torso. Biopsy demonstrated inflammation of the parenchyma with neutrophils, mononuclear cells, plasma cells, and occasional eosinophils, with focal parenchymal necrosis and mild cholestasis	Following cessation of the turmeric supplement (on presentation), her liver function tests improved dramatically within a fortnight Complete resolution in less than 6 wks
7	Suhail et al/2020/N = 1	A 61-year-old female Underlying polycystic liver disease Turmeric supplements for 6 months Hepatitis associated with polyarthralgia Hepatocellular type of liver injury Autoimmune antibody (ANA) was positive Biopsy showed pan lobular hepatitis with early parenchymal collapse suggestive of acute hepatitis and hepatocellular pattern of injury along with ceroid-laden macrophages	Turmeric supplements were discontinued, and the hepatitis resolved in 21 d with steroid treatment No recurrence of hepatitis during the follow-up period

TABLE 1. (*continued*)

No.	Author/year/patients	Liver injury and associated features	Clinical outcomes and comments
8	Lee et al/2020/N = 1	A 55-year-old woman Underlying Hashimoto's thyroiditis, autoantibody (ANA) strongly positive Qunol Liquid Turmeric 15 mL daily for 90 d Liver biopsy showed interface hepatitis with a mixture of plasma cells, lymphocytes, eosinophils, and neutrophils and features were consistent with autoimmune hepatitis	Withdrawal of turmeric supplement drastically improved liver tests and complete resolution of hepatitis in 1 mo without recurrence of hepatitis No immunosuppression therapy started Case highlights triggered autoimmune hepatitis due to turmeric (herb-induced autoimmune hepatitis)
9	Sohal et al/2021/N = 2	Both women—first, over-the-counter supplement containing turmeric 2000 mg and black pepper daily for 3 mo for back pain; second, turmeric tablets 2 times a day, duration unknown Hepatocellular type of liver injury Liver biopsy in first revealed hepatocyte ballooning and necrosis, with an absence of periportal necrosis, steatosis, or fibrosis and in the second, done 2 mo after the initial presentation, nonspecific patchy, predominantly mononuclear portal inflammation without readily identifiable interface activity and clusters of ceroid-laden macrophages Autoantibody ANA was positive in the second patient	Complete resolution in 6 mo in the first patient and within 1 mo in the second patient
10	Lombardi et al[89]/N = 7	Records of Tuscan cases of acute hepatitis were obtained from the Italian Phytovigilance system In all cases, hepatotoxicity was associated with Curcuma longa formulations with high bioavailability and high dosage of curcumin/curcuminoids Predominantly in females (6/7), time to onset 1–8 mo, positive de-challenge successful in 5/7 patients Doses ranged from 400 mg to 1000 mg of whole turmeric extracts, 1–4 tablets a day	In the 23 cases identified through the systematic review, most patients were concomitantly exposed to at least one other medication None of the patients died, and all improved with the withdrawal of the offending herbal supplement and supportive care
11	Prisca et al/2022/N = 1	A 62-year-old female with a history of hypertension Consumption of turmeric tea over the preceding 3 weeks Hepatocellular type of liver injury Liver biopsy was not performed, and the dose of turmeric tea consumption was not delineated	The patient improved with turmeric cessation, with complete resolution of abnormal liver enzymes on follow-up
11	Sunagawa et al/2022/N = 1	A 49-year-old woman with a history of ocular hypertension, polycystic ovarian syndrome Two capsules of turmeric supplement (1000 mg containing 950 mg curcuminoids and 10 mg black pepper) for 1.5 mo Hepatocellular type of liver injury A liver biopsy was not performed	Follow-up visit 71 d after the initial presentation demonstrated complete resolution of her jaundice and liver chemistries No immunosuppressive therapies were initiated at any point during her treatment.
12	Ajitkumar et al/2023/N = 1	A 55-year-old woman Alcohol use, 2 glasses of wine daily for 30 y, last intake 5 d before jaundice onset Turmeric supplements 1500 mg once daily for wrist pain for 1 mo No liver biopsy was performed	Spice withdrawal along with i.v. n-acetyl cysteine infusion resolved symptoms and ameliorated liver test abnormalities Her liver function tests normalized 2 mo after her initial presentation
13	Smith et al/2023/N = 1	A 62-year-old female with hypertension Drank turmeric tea for 3 wks before symptom onset (dosage not identified) No liver biopsy was performed	The patient improved clinically with turmeric cessation, and her liver enzymes returned to normal range upon follow-up after 1 mo.
14	Halegoua-DeMarzio et al[91]/ N = 10	Eight were women, and the median age was 56 y Liver injury was hepatocellular type in 9 patients and mixed in 1 Liver biopsies in 4 patients showed acute hepatitis or mixed cholestatic hepatic injury with eosinophils Chemical analysis confirmed the presence of turmeric in all 7 products tested; 3 also contained piperine (black pepper)	Five patients were hospitalized, and 1 patient died of acute liver failure HLA typing demonstrated HLA-B*35:01 as a risk factor Turmeric causes potentially severe liver injury that is typically hepatocellular, with a latency of 1 to 4 mo and strong linkage to HLA-B*35:01

Abbreviations: ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies.

treatment with a brief course of corticosteroids. However, there have been reports of fatalities resulting from acute exacerbation of preexisting cirrhosis and the requirement for liver transplantation among patients diagnosed with ALF.[96] Consumers and patients must know for a fact that Giloy (Table 2) may, particularly for individuals with diagnosed or asymptomatic autoimmune disorders or those who are at risk of developing such diseases, exacerbate underlying autoimmune liver disease or worsen silent autoimmune hepatitis.

Withania somnifera (Ashwagandha)

Withania somnifera, often known as ashwagandha (Indian Winter Cherry or Indian Ginseng), is a key ingredient in traditional Ayurvedic remedies. It is classified as a Rasayana (or health-promoting "tonic") in traditional Ayurvedic scriptures and is used to treat a variety of diseases.[102] Despite being used as a medicinal herb for a wide range of claimed health benefits and therapeutic effects, there is a general lack of clinical evidence from well-designed and rigorously performed studies that conclusively prove that Ashwagandha is safe or effective for use in preventive or therapeutic health care.[103] Ashwagandha predominantly contains the bioactive compound steroidal lactone triterpenoids, commonly known as withanolide. The first case of Ashwagandha-induced liver injury was reported in a 20-year-old male with anxiety.[104] A liver biopsy revealed severe intrahepatic cholestasis with extensive canalicular bile plugs. A study from Iceland and US-DILIN described 5 individuals with a mean age of 43 years who developed cholestatic jaundice 2–12 weeks after taking Ashwagandha supplements. Liver biopsy indicated severe cholestatic hepatitis. The clinical course lasted for 5–20 weeks, and there were no cases of hepatic failure. Chemical analysis of the recovered products confirmed the presence of Ashwagandha and the absence of competing hepatotoxic compounds or conventional drugs.[105] The Liver Research Club India group published the most extensive series of Ashwagandha-related DILI.[106] Out of the 23 patients, the investigators identified 8 cases caused by a single-component formulation. Most of the participants were men, and the most common presentation was cholestatic hepatitis. During follow-up, 3 patients with ACLF and 3 with underlying chronic liver disease died. Histopathological examination of the liver revealed cholestatic hepatitis along with portal-based inflammation induced primarily by lymphocytes and eosinophils, and in most instances, severe hepatocellular necrosis. On follow-up, 1 patient developed chronic CAM-DILI. Once thought to be uncommon, Ashwagandha-related CAM-DILI is now being reported frequently from all over the world because of its increased marketing as a dietary supplement based on ambiguous data.

The Netherlands Pharmacovigilance Center Lareb reported 4 cases of Ashwagandha-related DILI in patients who took the herb as an anxiolytic in the form of dietary supplements, while the World Health Organization pharmacovigilance database Vigibase recorded 15 cases of Ashwagandha-related liver injury.[107] The Hepatotoxicity of Ashwagandha is potentially due to withanolide, which causes irreversible adduction to hepatocellular DNA and subsequent cellular damage, resulting in glutathione depletion, cytotoxicity, and thus, liver damage.[108] In 2020, the Technical University of Denmark conducted various risk assessments of Ashwagandha in dietary supplements and determined that, based on existing evidence, no safe lower limit for consumption could be established. Aside from its proven liver toxicity profile, Denmark prohibited Ashwagandha based on this investigation because of its possible harmful effects on hormones and capacity to induce abortion. Sweden (followed by Germany) determined that the Danish risk assessment may also be implemented in their respective regions, raising the prospect that additional European Union member states may ban the marketing of Ashwagandha-based products.[109,110] In summary (Table 3), formerly thought to be rare, reports of CAM-DILI caused by Ashwagandha are increasing worldwide, with afflicted patients typically presenting with a protracted course of cholestatic hepatitis and a higher risk of mortality in those with preexisting liver disease.

BENEFICIAL CAM FOR THE LIVER—SEPARATING FACT FROM FICTION

Silybum marianum (Milk thistle)

Silymarin is a botanical extract obtained from desiccated seeds and fruits of the milk thistle plant (Silybum marianum). Silymarin extract consists of an intricate mixture of phytochemicals, predominantly flavonolignans, flavonoids (taxifolin and quercetin), and polyphenolic compounds. These substances are antioxidants and anti-inflammatory agents and have several additional biological roles, as demonstrated in preclinical research. The main constituents of silymarin are 4 flavonolignan isomers: silybin, isosilibinin, silichristin, and silidianin. Among these, silybin is the most abundant and biologically active. Silybin, which is composed of 2 diastereomers, silybin A and silybin B, makes up around 50-60% of the silymarin extract. The writings of Dioscorides, a Greek physician and botanist, outlined the medical advantages of silymarin, originally promoting it as a snakebite treatment. The English herbalist Nicholas Culpepper recommended the use of milk thistle throughout the sixteenth century to treat jaundice and eliminate gallbladder stones. In the 18th century, a German doctor

TABLE 2 Pertinent studies on *Tinospora cordifolia* (Giloy)-related liver injury

No.	Author/year/patients	Liver injury and associated features	Clinical outcomes and comments
1	Nagral et al[95]/N = 6	Liver injury was predominantly in women, 4 patients had underlying chronic liver disease The Median duration of consumption of herbs as fresh plant or proprietary tablet formulation was 90 d Various types of autoantibodies related to liver disease strongly positive Hepatocellular and cholestatic mixed pattern with autoimmune hepatitis-like features with lymphoplasmacytic inflammation along with eosinophils, varying grades of interface hepatitis and necrosis	One patient with acute-on-chronic liver failure died the majority were on long-term immunosuppression therapy Giloy herb unmasked autoimmune hepatitis in those with silent disease and triggered autoimmune hepatitis in those at risk for autoimmune liver disease
2	Gupta et al[99]/N = 2	One male and 1 female One consumed fresh plant and the other in the form of pellets available over-the-counter from market Various types of autoantibodies related to liver disease strongly positive Hepatocellular and cholestatic mixed pattern with bridging or submassive necrosis	One patient developed acute liver failure and underwent liver transplantation Catastrophic liver failure associated with short-term use of Giloy herb in persons without additional risk factors
3	Parikh[100]/N = 2	Both females Consumed capsules of Giloy herb extracts available in the market Various types of autoantibodies related to liver disease strongly positive Liver injury was associated with lymphocytic inflammation with necrosis and severe interface hepatitis	Short course of immunosuppression therapy led to the complete resolution of acute hepatitis Giloy herb can trigger de-novo autoimmune hepatitis, which requires finite treatment with immunosuppressive agents
4	Gupta et al.[97]/N = 2	Both women Various types of autoantibodies related to liver disease strongly positive Consumed fresh plant boiled water decoction and commercially available Giloy herb tablets for 1 mo Biopsy showed expanded portal tracts and interface hepatitis with moderate mixed inflammatory infiltrates comprising neutrophils, eosinophils, plasma cells, and lymphocytes and varying severity of liver cell necrosis	Both patients improved with a short course of steroids without any relapse of autoimmune liver disease on follow-up up The importance of herb-induced autoimmune hepatitis compared to flare of primary autoimmune hepatitis is emphasized
5	Sahney et al/2022/N = 3	Authors discuss 3 severe cases out of suspected 25 cases due to Giloy herb-induced liver injury All 3 were women, in whom 2 had underlying autoimmune disorders (hypothyroidism and systemic lupus) Liver injury was hepatocellular or mixed and associated lymphoplasmacytic infiltration, numerous eosinophils and in portal tracts and interface hepatitis	All survived; 1 patient was on long-term immunosuppression due to underlying chronic liver disease. One needed only withdrawal of the offending herb that resulted in spontaneous resolution of hepatitis
6	Gupta et al/2022/N = 3	Two females and 1 male All had hepatocellular pattern of liver injury Intake of branded tablets of giloy herb extract or home-made boiled herb decoctions No liver biopsy was performed, and all patients were managed with symptomatic care only	All patients survived with resolution of hepatitis only on withdrawal of the offending herb Corticosteroids were not used, but hepatitis resolution and recovery time were prolonged The immunomodulatory properties of Giloy herb can lead to autoimmune-like illness in predisposed persons and trigger autoimmune liver disease in at-risk groups
7	Rastogi et al/2022/N = 2	Two patients without any underlying comorbidities or known chronic illness Giloy used for 2–4 wk duration, leading to severe jaundice and hepatitis Biopsy did not show features of autoimmune liver injury and revealed perivenular necrosis and mild portal infiltrate, no interface hepatitis, paucity of plasma cells, no rosettes, and relatively mild-moderate inflammatory infiltrate, predominantly with eosinophils	Both patients responded to a short course of steroids and ursodeoxycholic acid therapy One patient self-re-challenged with the Giloy formulation and developed new onset and fluctuating jaundice, which resolved spontaneously a second time also, but after a prolonged disease course

TABLE 2. (*continued*)

No.	Author/year/patients	Liver injury and associated features	Clinical outcomes and comments
8	Kulkarni et al[96]/N = 43	More than half of the cohort were females The median time from initial Giloy consumption to symptom onset was 46 d Patients presented with acute hepatitis, acute worsening of chronic liver disease (most common clinical presentation), or acute liver failure Liver biopsy revealed acute hepatitis with autoimmune features and hepatocyte and canalicular cholestasis and neutrophilic and eosinophilic infiltration	The largest published series of cases of Giloy-induced acute hepatitis Approximately 10% of patients died within 2 mo of presentation, and nearly 5% required liver transplantation within 90 d Analysis of retrieved Giloy samples did not reveal any competing hepatotoxic agents Positive autoimmune markers in acute (nonviral) hepatitis may indicate triggered or unmasked autoimmune hepatitis for which active reasons must be sought, and should include recent or long-term exposure to herbals containing Giloy
9	Nnamani et al[98]/N = 1	A 50-year-old female with autoimmune thyroiditis Consumed HistaEze™ supplement containing *Tinospora cordifolia* No liver biopsy was done	Short course of steroids significantly reduced hepatitis Liver injury resolved completely in 90 d
10	May et al/2023/N = 1	A 54-year-old woman without any comorbid illnesses Consumed Giloy powder along with other herbal drugs for 3 months for gastrointestinal complaints No liver biopsy was performed	Withdrawal of offending herbals resolved hepatitis spontaneously No steroids given, and only symptomatic care provided

named Johannes Gottfried Rademacher conducted experiments that showed the potential benefits of using "tinctures" made from milk thistle seeds to treat patients with liver disorders.[111]. Despite extensive research as a prophylactic "hepatoprotective agent," there are no definitive data supporting the effectiveness of silymarin in preventing or treating any liver disease.[111,112] However, the use of milk thistle seems to be both safe and well-tolerated. Nonetheless, there were no substantial changes in mortality rates, liver histology, or biochemical markers of liver function in patients with chronic liver disease.[113] Systematic reviews and meta-analyses of published studies have yielded inconclusive results. Initial studies have shown a minor decrease in elevated transaminase levels, improved survival in individuals with Amanita mushroom-related liver injury, and a reduced risk of liver injury due to anti-tuberculosis drugs.[114,115] Nevertheless, recent and extensive meta-analyses have revealed a lack of significant therapeutic advantages of silymarin in both acute and chronic liver illnesses, including alcohol-associated, non-alcohol–associated fatty liver, and viral hepatitis.[116–119] It is crucial for consumers to understand that milk thistle extracts found in the unregulated herbal supplement market are frequently contaminated with fungi and mycotoxins. These contaminants can potentially cause liver damage with the use of herbal-based dietary supplements.[120,121]

Phyllanthus niruri (Chanca piedra/Gale-of-the-wind/Bhumi amla)

Phyllanthus niruri is a traditional shrub of the genus Phyllanthaceae that has been used for centuries as a liver "support" agent and for the treatment of kidney stones in Ayurvedic therapies and TCM. Preliminary studies using cell, tissue, and animal models have shown various biological (hepatoprotective, antiviral, antibacterial, hypolipidemic, hypoglycemic, analgesic, anti-inflammatory, cardioprotective, anti-urolithic, and anti-hyperuricemic) properties associated with the bioactive compounds present in *Phyllanthus niruri*.[122] However, none of these "properties" have been conclusively translated into clinically relevant benefits for any liver disease condition. *Phyllanthus* was shown to have a positive effect on the clearance of hepatitis B markers without major adverse effects in decades-old studies; however, further clinical trials did not show clinically relevant benefits.[123] Thus, the use of *Phyllanthus niruri* for liver disease prevention and management is largely based on anecdotal literature and patient experiences; unscientific advertisements; and blind promotions from the alternative medicine industry and its practitioners, appealing to beliefs, faith, and tradition rather than science, logic, and reasoning. High-quality, validated, and replicated clinical trials on the use of *Phyllanthus niruri* in various liver disorders are lacking in the literature. Nonetheless, recent studies and assessments of available published data have shown a lack of clinically significant benefits for liver disease.[124,125]

Camellia sinensis (Green tea)

Similar to other herbal dietary supplements, green tea is marketed and endorsed for many purposes, such as preventing cancer and cardiovascular

TABLE 3 Pertinent studies on *Withania somnifera* (Ashwagandha)-related liver injury

No.	Author/year/ patients	Liver injury and associated features	Clinical outcomes and comments
1	Björnsson et al[105]/ N = 5	Liver injury was predominantly in men, with a mean age of 43 y Median duration of herb intake and symptom onset was 2–12 wk Pruritus and jaundice were the most common presentations Pain in the abdomen is a distinct feature Liver histology classically reveals cholestatic hepatitis	All patients survived and hepatitis resolved within 1-5 mo None developed chronic liver injury Recovery from cholestatic hepatitis was prolonged in most but without further clinical consequences
2	Ireland et al./2021/ N = 1	A 39-year-old female 154 mg of Ashwagandha root extract on alternate days for 6 weeks for anxiety No cholestatic symptoms at onset but later developed severe abdominal pain and itching Liver biopsy revealed features of a severe acute cholestatic hepatitis with confluent necrosis but no convincing signs of chronicity	Started on ursodeoxycholic acid, and symptoms abated in 2 weeks' time But complete resolution of jaundice was after a prolonged course No recurrence of symptoms
3	Weber et al/2021/ N = 1	Male 450 mg ashwagandha daily for 1 y and 20 d Severe cholestatic hepatitis No liver biopsy was performed	Complete resolution on withdrawing herbal supplement No recurrence or chronicity Authors also discuss close to 100 cases of self-reported adverse events related to ashwagandha use from product websites mainly featuring pruritus and abdominal pain symptoms
4	Sajjadh et al/2022/ N = 1	A 20-year-old male Jaundice, pruritus, and pain in abdomen OTC Ashwagandha 450 mg once daily for 30 d No liver biopsy was performed	Spontaneous resolution on withdrawal of offending herbal supplement OTC medication and herbal supplements containing Ashwagandha are unregulated, and caution must be exercised
5	Rattu et al/2022/ N = 1	A 44-year-old female Daily Ashwagandha supplement for "anxiety" Severe cholestatic jaundice with abdominal pain No liver biopsy was performed	Symptomatic care with cholestyramine improved liver tests, and hepatitis resolved in a few week's time No re-challenge was performed
6	Lubarska et al/2023/ N = 1	Male gender Consuming only ashwagandha for 1 y Progressive cholestatic jaundice, hospitalization after 90 d of symptom onset No liver biopsy was performed	Severe cholestatic symptoms and progressive and stormy course of jaundice Required therapeutic plasma exchange and i.v. steroids to improve liver tests and reduce symptoms Three months after treatment, hepatitis was resolved
7	Bokan et al/2023/ N = 2	Both women In the first case, ashwagandha capsules (450 mg, 3 times daily) for 6 mo; second case, 45 d of using ashwagandha capsules (450 mg) Severe cholestatic hepatitis without chronicity Elastography of liver showed no fibrosis	Improvement in liver enzyme levels 2 weeks after the cessation of ashwagandha capsules and complete normalization after 4 and 8 wks.
8	Vazirani et al/2023/ N = 1	A 48-year-old man Severe cholestatic liver injury—ashwagandha along with alcohol use Predominant symptom was pain in the abdomen followed by jaundice and pruritus Liver biopsy was not performed	Progressive improvement in symptoms and liver tests ensued after 2 wks Hepatitis resolved after 1 mo on only supportive care No recurrence of symptoms even though the patient relapsed on alcohol after 1 mo
9	Suryawanshi et al/ 2023/N = 1	A 41-year-old woman Prescribed unknown dose of ashwagandha and progesterone by a Naturopath for general well-being and improvement in quality of life after thyroid resection Severe progressive hepatocellular jaundice leading to acute liver failure, no cholestatic symptoms	First report to demonstrate acute liver failure due to ashwagandha supplements Patient survived after receiving a liver transplantation Extensive hepatocellular necrosis with acute hepatitis on liver histology

TABLE 3. (*continued*)

No.	Author/year/ patients	Liver injury and associated features	Clinical outcomes and comments
10	Tóth et al/2023/ N = 1	A 65-year-old woman Began to take ashwagandha because of "troubled thoughts" 4 wks before admission Liver biopsy revealed perivenular spotty hepatocellular necrosis, accompanied with multiple ceroid-laden macrophages, hepatocellular, and canalicular cholestasis	Following the withdrawal of the drug, the serum transaminase activities and serum bilirubin gradually dropped without any further specific therapy Only a symptomatic therapy with cholestyramine was administered on the second day due to pruritus Three months later, all liver tests were normal
11	Philips et al[106] N = 8	Only patients with ashwagandha single-ingredient formulation-related herb-induced liver injury included Male predominant Cholestatic hepatitis was the commonest presentation Liver biopsy revealed cholestatic features predominantly with hepatocellular necrosis and lymphocyte/eosinophil predominant portal-based inflammation Chemical analysis of retrieved formulations revealed only natural phytochemicals without adulteration or contamination	Largest series of ashwagandha-related liver injury in published literature Five patients had underlying chronic liver disease; 3 presented with acute-on-chronic liver failure, and all three died on follow-up One patient progressed to chronic herb-induced liver injury Ashwagandha-liver injury presents with cholestatic hepatitis and can lead to the syndrome of acute-on-chronic liver failure with high mortality in those with preexisting liver disease

illnesses. The purported benefits of being anti-inflammatory, anti-arthritic, antibacterial, antiangiogenic, antioxidative, antiviral, neuroprotective, and cholesterol-lowering are based on extrapolations from clinical studies of low-quality, vast, and diverse observational populations and preclinical research. The positive effects of green tea were ascribed to its predominant polyphenol, catechin, epigallocatechin-3-gallate (EGCG).[126] Nonetheless, metanalysis and systematic reviews on green tea and its health benefits have been largely inconclusive, while its positive effects (such as reduced risk of liver cancer or coronary heart disease with a minimum of 3–4 cups/day) remain exaggeratingly extrapolated from insignificant "trends."[127,128] Even though a statistically insignificant reduction in liver test abnormalities in patients with steatotic liver disease was identified, the worsening of liver tests in healthy subjects was also notable.[129] Recent studies on the effect of green tea on the liver have only shown "positive correlations" without conclusive evidence of benefits.[130–132] Interestingly, in the presence of dwindling data on its benefits, increasing reports on green tea-related liver toxicity (mostly extracts and supplement formulations) have been on the rise. Preclinical and clinical evidence for green tea-related hepatoxicity is well-documented in the medical literature, with reports ranging from asymptomatic elevation of transaminase levels to severe liver injury resulting in ALF leading to death or liver transplantation. Studies from the US-DILIN have shown that liver injury is typically hepatocellular, with a close association with HLA-B*35:01, suggesting an idiosyncratic and immune-mediated pathophysiology, with marked serum aminotransferase elevations and symptomatic presentation with jaundice in the majority. More than one-third of patients require liver transplantation, and in rare cases (< 5%), green tea hepatotoxicity may progress to chronic liver injury.[92,133]

Coffea arabica (Coffee)

Coffea is a genus of flowering plants belonging to the family Rubiaceae. Two out of 120 species are commonly cultivated as one of the most valuable and widely consumed and traded beverages: *Coffea arabica* (Arabica), which accounts for 60%–80% of the world's coffee production, and *Coffea canephora* (Robusta), which accounts for ~20%–40%. Over the last 2 decades, an increasing number of epidemiological and experimental studies have proven the benefits of coffee in chronic liver disorders. The presumed beneficial bioactive compound in coffee is the polyphenol chlorogenic acid and not caffeine, which is why studies analyzing the effects of decaffeinated coffee beverages have demonstrated positive effects on steatotic liver disease.[134] An umbrella and systematic review showed that coffee consumption (black, no sugar, a minimum of 3 cups/day) reduced the risk of fibrosis progression in metabolic syndrome–associated steatotic liver disease, while another meta-analysis showed that it was significantly associated with a 35% decrease in the odds of significant liver fibrosis.[135,136] Contrary to previous findings, recent studies have shown that coffee consumption is associated with lower liver stiffness but not steatosis.[137] Nonetheless, even though coffee consumption was found to be associated

with a lower incidence of steatohepatitis, hepatic fibrosis, and HCC, the molecular mechanisms underlying these favorable effects remain unknown. Larger prospective controlled trials and research on unique bioactive phytocompounds in coffee might help us to better understand the mechanisms underlying its liver-protective properties. Since there have been no adverse events reported from coffee consumption on the liver, and a large body of observational and experimental evidence points towards benefits on the liver and metabolic parameters, current consumers need not be advised to refrain from including coffee as part of their routine diet.

A multitude of products are advertised, promoted, and sold online and offline through print, visual, and social media under the garb of "liver protector," "hepatoprotective supplement," and "liver detox." The clinically relevant, tested, and validated benefits of CAM and HDS are either nonexistent or based on weak preclinical evidence. While some may seem benign, others have a high likelihood of causing severe liver injury, contrary to what is claimed on the label (Figure 3).

CHALLENGES AND FUTURE DIRECTIONS

The global CAM market is predicted to grow at a compound annual growth rate of 23.77% during the forecast period 2023–2032.[138] With the evolution of

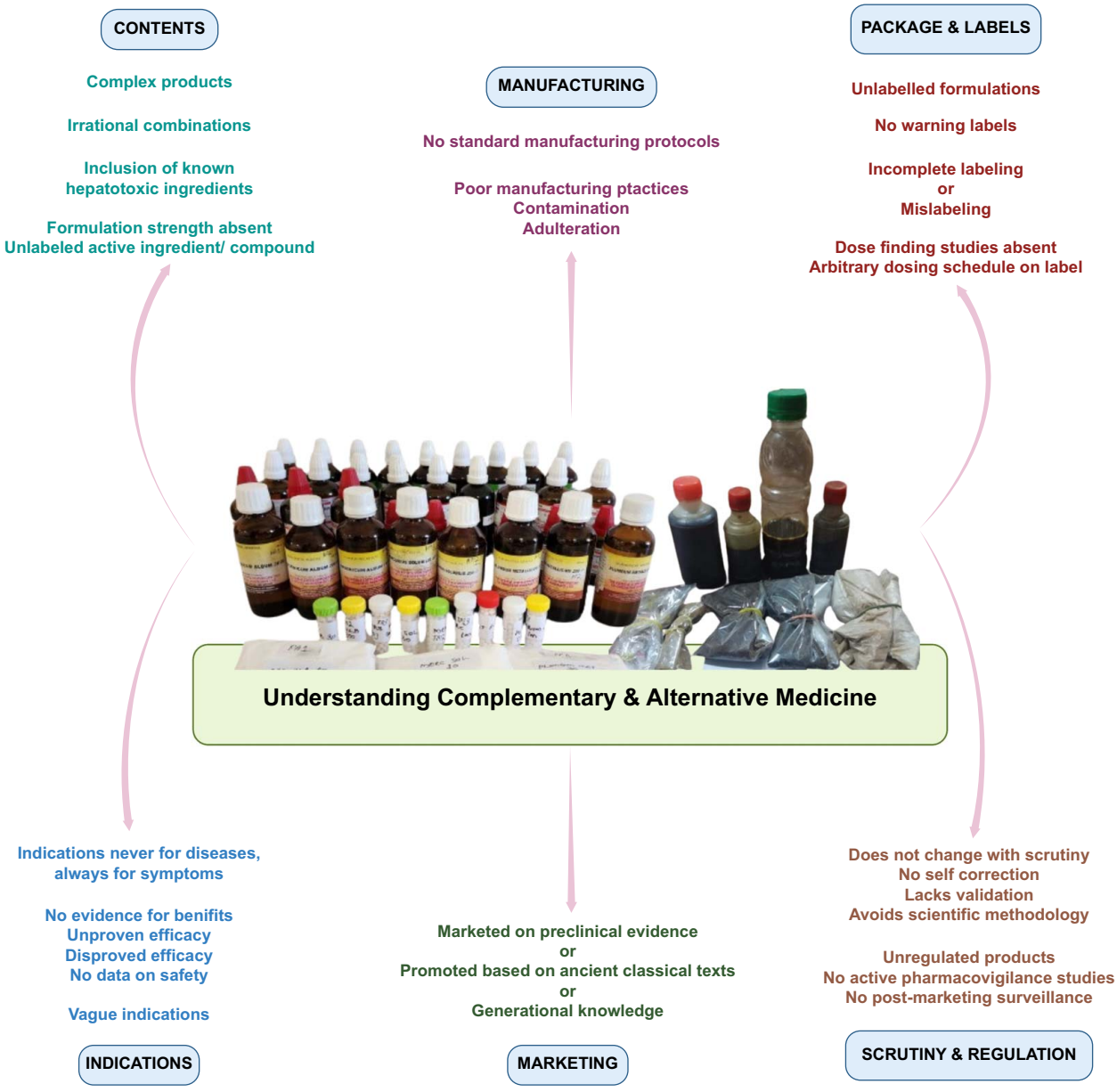

FIGURE 3 Salient features of complementary and alternative medicines for both physician and patient knowledge.

social media-related health information and easy access to "health influencers," the use of CAM products or practices is on the rise, and hepatologists across the globe must accept the fact that CAM-DILI will be increasingly identified and reported. This is evident from the fact that ALF due to DILI caused by prescription drugs has been on the decline, whereas those due to traditional medicines and HDS are on the rise.[139] There has also been an 8-fold increase in HDS-related liver failure, leading to transplant waiting over the last quarter century in the United States.[140] Elsewhere, many patients with CAM-related liver injuries remain undiagnosed or misdiagnosed.

Physicians must understand that CAM therapies are here to stay and, responsible and reasonable, and reasonable dissemination of information and knowledge on evidence-based practices for health-seeking behavior will help improve scientific temperament among the public and patients regarding alternative medicine therapies.[141] Physicians should ask patients regarding their use of CAM products or practices mandatorily as part of their clinical history without prejudice and respecting the patient's options, choices, and decisions. When physicians openly and empathetically discuss, debate, teach, and reassure patients about CAM-based health-seeking behaviors, the trend towards seeking health care from an evidence-based scientific perspective improves.[142] Similarly, patients must be open to disclosing their use of CAM-related products and practices to physicians to improve their preventive or therapeutic advice.

The takeaway message for both the physician and patient communities is that "herbal does mean natural, but not always safer," and that avoidable disease burden due to CAM could be minimized with open dialogues, nonjudgemental, and rational conversations. Physicians must be able to identify commonly and currently prevalent harmful health misinformation, especially in the context of CAM among the public and patients and their families, on a routine basis and approach it using the "actionable, factual and (un) verifiable" algorithm to diffuse harmful outcomes.[143] Perceiving gaps in patients' knowledge and providing proactively constructive criticism instead of denigrating misinformed choices can help improve health literacy in the context of CAM-related health-seeking behavior. For example, provide information proactively about the lack of clinical benefits and hepatotoxicity of green tea extracts as weight loss supplements to an obese patient with chronic liver disease during conversations on lifestyle changes.

Clinical departments, hospitals, institutes, and multicenter collaborative networks must invest time, resources, and personnel to create adequate capture of DILI from conventional drugs, as well as CAM to pragmatically monitor toxicity from unregulated and misinformed use of such products and practices.

A large volume of CAM products and practices are based on and driven by pseudoscientific principles and, therefore, cannot be tested under standardized, validated, and falsifiable scientific clinical research protocols; hence, personnel and financial resources must not be wasted on such futile attempts.[144] Nonetheless, rational and well-reasoned trials should be designed to test bioactive compound(s) of interest in difficult-to-treat but commonly encountered liver diseases or symptoms of liver disease. These trials must be based on valid hypotheses and adequately generated theories from well-designed preclinical studies and strong in methodology with pertinent, and clinically relevant objective outcome measures.

Drug discovery by rational assessment and scientific reasoning based on traditional medicine knowledge could help identify novel compounds of natural origin that may prove useful in the future. Until then, historical, traditional, and cultural aspects of health care must be preserved in memoriam, and reasonable search within traditional knowledge databases must be performed actively to identify novel therapeutics. CAM-related liver injury is mostly idiosyncratic but difficult to diagnose and treat due to the complexities of implicated products and other underlying disease conditions in the patient. Improving the scientific temperament and critical thinking in the context of the public's knowledge and perceptions of CAM could help reduce the rising (but avoidable) liver disease burden across the globe.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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