Review Article

A narrative review of herb-induced liver injury

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Abstract: Herb and herbal product have been used for both healthy and specific ailments. Its use as medicine or dietary supplements has increased worldwide for more than a decade due to easy access, purported harmless nature, and perceived therapeutic efficacy. Herb induced liver injury which has been recognized for many years is likely to increase. Close scrutiny on herb related safety and liver toxicities is strongly advocated. Toxic ingredients, reactive metabolites, organelle stress, bile salt export inhibition and immune response have been postulated in the pathogenesis of herb-induced liver injury (HILI). HILI is in analogy to drug induced liver injury (DILI) in following aspects (I) clinical manifestations: from asymptomatic abnormal liver tests to severe liver injury and liver failure requiring liver transplantation; (II) mechanism: idiosyncratic or intrinsic; and (III) phenotypes of injury: hepatocellular, cholestatic or mixed type. The diagnosis of HILI remains a challenge. Roussel Uclaf Causality Assessment Method (RUCAM), a structured, quantitative, effective and validated tool for HILI should be reinforced in clinical use. The pathogenetic hallmarks of genome-wide association study (GWAS), human leukocyte antigen (HLA) alleles and non-HLA genetic variants may determine the risk for HILI. Diagnostic biomarkers for HILI need to be re-investigated and reliably validated in future research for their clinical implications. Global prospective HILI registry with advances in the exploration of toxic ingredients, genetic testing and new biomarkers may better explain the pathogenesis and pathogenetic mechanism of HILI which can lead to improvement in diagnosis and treatment of DILI. Pharmacovigilance and standardized regulatory surveillance on safety and efficacy of herbs and herbal products are warranted to reduce the occurrence of HILI and its associated morbidity and mortality.

Keywords: Herb induced liver injury; herb hepatotoxicity; herb associated liver injury

Received: 21 January 2021; Accepted: 08 June 2021; Published: 30 June 2021.

doi: 10.21037/dmr-21-8

View this article at: https://dx.doi.org/10.21037/dmr-21-8

Background

The use of herbs as medicine or products has increased worldwide for more than a decade (1-4). Herbal products are frequently used by humans for different reasons to improve their health (1,5).

Although herbs and herbal products may have benefits for health, they also can develop adverse reactions. The rise in consuming herbs is likely due to easy access, purported harmless nature, and perceived therapeutic efficacy (2,6-8). Hepatotoxicity from herbs has been recognized for many years. The true incidence of herb-induced liver injury (HILI) is not easily determined due to the likelihood of underestimation and underreporting (9-11). There are various factors either host dependent or herb dependent that affect the clinical features and severity of HILI (10,12). HILI is diverse and classified as hepatocellular, cholestatic or mixed injury with varying clinical manifestations from asymptomatic elevation of liver tests to fulminant hepatitis, and fatal liver injury requiring liver transplantation (1,3,10,12). The true pathogenesis of each HILI is not fully understood which requires further elucidation. The diagnosis of HILI is an exclusion of other liver diseases. Roussel Uclaf Causality Assessment Method (RUCAM) has been most but not all used in causality assessment of HILI in clinical practice (9,11-14). The development of genetic

testing is in progress which may predict risk for HILI and assist its early diagnosis. The exploration of definitive and valid biomarkers for HILI remains of high interests since it may help monitoring the severity, and outcome of HILI (14).

This review attempts to gather current medical knowledge of relevant and established information of HILI and advocate regulatory measures in the use of herbs and herbal products for public safety.

I present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-8).

Objectives

(I) To review current knowledge of clinical manifestations, diagnosis and management of HILI;
(II) To advocate the policy development in global standardization of pharmacovigilance in the use of herbs and herbal products.

Methods

Literature search was conducted through PubMed database of publications in English including retrospective, prospective studies, meta-analysis, case reports, case series, expert opinions and reviews, from different countries including but not limited to the United States (US), from year 1988 to 2020.

Discussion

Hepatotoxicity from herbs has been recognized for many years. Herbal products are categorized differently from pharmaceutical drugs and the safety profile is not regulated by standard measures. The true incidence of HILI is not easily determined due to the likelihood of underestimation and underreporting (9-11). A population-based study in Iceland at earlier time described 16% of DILI cases were due to use of herbal dietary supplements (15). HILI may have a more serious impact on different regions in the world (16). Publications between 2007 and 2013 from several Asian countries showed that prevalence of traditional medicines and dietary supplements induced liver injury ranging from 17.1% in Japan, 18.6% in China, 71% in Singapore to 72.7% in Korea respectively (17-20).

Although a retrospective study of 25,927 hospitalized DILI patients in mainland China from 2012 to 2014 showed that traditional Chinese medicines (TCM) or HDS accounted for 26.8% (21), the study was challenged by lacking rigorous entrance criteria with potential over-diagnosis, not accurately classified by causality assessment, and uncertain temporal link of medication use to liver injury given its retrospective design (22). The frequency of HDS induced liver injury in Drug Induced Liver Injury Network (DILIN) in the US remained stable around 20% (23). HDS in a retrospective cohort study in the US represented 18.8% of acute liver failure (24). A more recent systemic review of 31 studies described that HILI represented 25% of the DILI (25).

Clinical characteristics

Medicinal herbs or herbal products are originated from different parts (leaf, root, stem and flower) of the plant (2). There are various factors affecting the clinical features and severity of HILI, (I) herb associated: dose, duration, metabolism, misuse, abuse, purity, contaminant, adulterant, mislabeling and un-labeling; (II) host associated: gender, age, genetics and underlying liver disease (10,26-28).

Clinical manifestations of HILI vary from mild asymptomatic elevated liver tests, to acute hepatitis or fulminant hepatitis with liver failure requiring liver transplant, or chronic hepatitis (1,3,27,29-33). Pattern of HILI is classified as hepatocellular, cholestatic or mixed injury by R ratio based on liver biochemistry of alanine aminotransferase (ALT), and alkaline phosphatase (ALP). R = (ALT/ULN)/(ALP/ULN) (R >5 hepatocellular, 2–5 mixed pattern, <2 cholestatic) (10,12,27).

There are hundreds of medicinal herbs or products linked to different degrees of HILI per meta-analysis, reviews, case reports, case series over past 2–3 decades. Well-established HILI is listed in *Table 1*.

HILI presents more frequently with hepatocellular injury (75,76). It appears more prevalent in women as compared to men (75,77) but a study from China comparing HILI to DILI described that HILI from TCM affected a smaller portion of females (76).

Mechanism and pathogenesis

The true pathogenesis of HILI is not quite understood. Toxic ingredients, reactive metabolites, endoplasmic reticulum and mitochondrial stress, bile salt export inhibition have been postulated in the pathogenesis of HILI causing hepatocyte necrosis, apoptosis and lead to activation of adaptive immune response (12,27,78).

Table 1 Herbs and types of liver injury

Herbs or *herbal products containing	Liver injury and significant severity
Unsaturated pyrrolizidine alkaloids (7,34-37)	Hepatic sinusoidal obstruction syndrome or veno-occlusive disease
Germander teucrium (26,38-41)	Hepatocellular, fatal liver failure
Atractylis gummifera (42-44)	Hepatocellular, fatal liver failure
Greater celandine (45-48)	Hepatocellular with jaundice
Piper methysticum, *Kava kava (49-53)	Fulminant hepatitis, liver transplant or fatality
Garcinia cambogia, *Herbal life, Hydroxycut (54-62)	Acute hepatitis, liver failure, liver transplant
Green tea extracts (63-67)	Acuate hepatitis, liver failure
Mitragyna speciosa, *Kratom (32,68-70)	Acute mixed hepatocellular and cholestatic liver injury
Catha edulis, *Khat (32,71-73)	Acute liver injury, liver failure, liver transplant or chronic liver disease
Several Asian medicinal herbs such as Ma Huang, Jin Bu Huan, Sho-Saiko-To (Xiao-Chai-Hu-Tang complex preparation), Dai-Saiko-To, Chaso and Onshido, Boh-Gol-Zhee, Shou-Wu-Pian and Linghzi (12,27,74)	Well established liver injury which vary in severity

Nevertheless, HILI manifests as idiosyncratic, or intrinsic liver injury. Idiosyncratic liver injury is not predictable or dose dependent, and it has a variable or long latency. Intrinsic liver injury is more predictable, experimentally reproducible, dose dependent, with a short and consistent latency period and higher incidence in humans (12,27,78).

Hepatic microsomal cytochrome P450 was shown involving in activation of pyrrolizidine alkaloids (PAs) in experiments of TCMs containing unsaturated PAs (79). Germander toxicity has been reproduced in animal experiments and transferred to human hepatotoxicity. Its toxicity is due to reactive metabolites from oxidization of neoclerodane diterpenoids through CYP3A isoform which deplete cytoskeleton associated protein thiols and hepatic glutathione leading to apoptosis of hepatocytes (80,81).

Diagnosis and causality assessment

The diagnosis of HILI remains a challenge. HILI is an exclusion of diagnosis when all alternative etiologies of liver injury such as acute viral hepatitis, autoimmune, hereditary, metabolic liver disease, ischemic hepatopathy and vascular disorder are completely ruled out (12,23,27,29,78,82).

RUCAM, a structured, quantitative, effective, and validated tool for causality assessment, is most but not all used in causality assessment of HILI in clinical practice (11-13,78,82-88). RUCAM algorithm includes 7 criteria. They are latency (time to onset), course after de-challenge, risk factors (age, alcohol/pregnancy), concomitant medications, exclusion of other etiologies, previous data on drug hepatotoxicity and response to re-challenge. The scores for each category are 0 to +2, –2 to +3, 0 to +2, –3 to 0, –3 to +2, 0 to +2, and –2 to +3, respectively. Total score ≤2: unlikely, 3–5: possible, 6–7: probable, ≥8: highly likely for liver injury (89,90).

Serum miRNAs were demonstrated as potential biomarkers with high sensitivity and specificity for diagnosis of HILI in rats (91). Biomarker research has been of great interests in improving the diagnosis of HILI. However, European Medicines Agency (EMA) and US Food and Drug Administration (FDA) officially retracted the Letter of Support affecting all biomarkers due to a significant scientific misconduct and fraud in the incriminated biomarker. This conceivably has had significant impact on biomarker research and development (92). Future exploration and validation of potential diagnostic biomarkers for HILI remain needed (22,92).

Genetic testing of human leukocyte antigen (HLA) alleles has been used in diagnosis of HILI. HLA-B*35:01 was shown to be a potential biomarker for *Polygonum multiflorum* (a Chinese herbal medicine) induced liver injury (93). A strong association of HLA-B*35:01 with green tea related idiosyncratic and immune mediated liver injury was recently published as well (94).

Management and outcomes

HILI is often self-limiting after offending herb or herbal

product is discontinued (95-98). Majority of the patients with mild to moderate liver injury will have gradual recovery. Close monitoring of signs and symptoms of severe liver injury such as hepatic decompensation or liver failure is essential. A retrospective study of 488 patients with HILI showed that 14.1% developed chronic HILI and 4.1% had acute liver failure with death or requiring liver transplantation (99).

Liver transplantation is indicated in severe HILI with acute liver failure (100). A retrospective study of 30 patients from 2007 to 2012 also implied that Chinese medicinal herbs caused 60% mortality in acute liver failure without liver transplantation (101).

Summary

The use of herbal medicine and products continues to rise globally despite the potential of significant liver injury. The diagnosis of HILI remains challenging. It is crucial for health care providers to raise the awareness of HILI for early diagnosis and proper management. RUCAM, a structured, quantitative, effective and validated tool for causality assessment in HILI should be reinforced in clinical use.

Further research in analysis of toxic ingredients of herbs on hepatocytes and the associated injury may better elucidate the pathogenesis of HILI. The development of pathogenetic hallmarks of GIWAS, HLA alleles and non-HLA genetic variants to identify risk for HILI; along with future exploration of specific and valid new biomarkers for early diagnosis of HILI are critical. Global prospective HILI registry including HILI related issues is essential for more definitive diagnosis, better management and favorable outcomes.

Furthermore, policy development and clinical implementation of standardized regulatory surveillance and pharmacovigilance on efficacy and safety of herbs and herbal products are warranted to ensure public safety and reduce HILI associated morbidity and mortality as well.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/dmr-21-8

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/dmr-21-8). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-21-8
Cite this article as: Lee TP. A narrative review of herb-induced liver injury. Dig Med Res 2021;4:28.