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Drug-induced liver injury

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Drug-induced liver injury (DILI), including herbal and dietary supplement hepatotoxicity, is often passed lightly; however, it can lead to the requirement of a liver transplant or may even cause death because of liver failure. Recently, the American College of Gastroenterology, Chinese Society of Hepatology and European Association for the Study of the Liver guidelines for the diagnosis and treatment of DILI have been established, and they will be helpful for guiding clinical treatment decisions. Roussel Uclaf Causality Assessment Method scoring is the most commonly used method to diagnose DILI; however, it has some limitations, such as poor validity and reproducibility. Recently, studies on new biomarkers have been actively carried out, which will help diagnose DILI and predict the prognosis of DILI. It is expected that the development of new therapies such as autophagy inducers and various other technologies of the fourth industrial revolution will be applicable to DILI research.

Keywords: Diagnosis; Drug-induced liver injury; Herb; Management

Introduction

In a narrow sense, drug-induced liver injury (DILI) deals with liver injury caused only by drugs. Herb-induced liver injury can be described as hepatotoxicity caused by herbal medicines other than drugs, but it is named herbal and dietary supplement (HDS) hepatotoxicity as a comprehensive concept that includes herbal medicine, health food, and folk remedies. In general, DILI is a liver injury caused by over-the-counter drugs, herbal medicines, health foods, folk remedies, and environmental hormones, as well as by a wide range of prescription drugs including HDS.

Although DILI is a concern in several clinical fields, it is often overlooked. DILI can progress into a chronic liver injury that lasts more than six months and can reach hepatic failure, which requires liver transplantation, or death [1-4].

Further, DILI not only hurts the health of the patient, but also has very serious personal, social, and national problems, including the financial burden of payment for treatment, loss of insurance finances, distrust of prescription doctors, medical disputes surrounding compensation issues, and the withdrawal of drugs developed by investing enormous amounts of time and money from the market [5,6].

Therefore, basic knowledge and recent research trends about DILI are introduced.

Guidelines for drug-induced liver injury

In 2014, the American College of Gastroenterology (ACG) first established the ACG guideline, a diagnostic and treatment guideline for the idiosyncratic DILI [7]. It presents an evidence-based approach for the diagnosis and management of DILI with special emphasis on DILI caused by HDS and DILI occurring in individuals with underlying liver disease. In 2017, the Chinese Society of Hepatology (CSH) established the CSH guideline, a diagnosis and treatment guideline for DILI that covers 16 evidence-based recommendations on diagnosis, differential diagnosis, treatment, and prevention of DILI [8]. Recently, the 2019 European Association for the Study of the Liver guideline presenting the available

evidence on risk factors, diagnosis, management, and risk minimization strategies for DILI was also established [9].

Online information resource on drug-induced liver injury

The liver disease research branch of the National Institute of Diabetes and Digestive and Kidney disease, in collaboration with the National Library of Medicine and Drug-Induced Liver Injury Network (DILIN), has developed an online resource for information on DILI resulting from prescription and over-the-counter drugs as well as from complementary and alternative medicines such as HDS. The web-based resource called "LiverTox," provides up-to-date, accurate, and easy-to-access information about the diagnosis, cause, prevalence, pattern, and management of DILI (http://livertox.nih.gov). China also provides a web-based resource called "Hepatox" on DILI (http://hepatox.org); however, it is not very helpful as it is only in Mandarin.

Definition of drug-induced liver injury and categorization according to R-ratio

DILI is defined as a liver injury caused by various drugs, herbs, or other xenobiotics leading to abnormalities in liver function. Terms such as hepatitis, liver cirrhosis, and liver necrosis should be used only to support liver biopsy findings; the term liver injury should be used if biochemical abnormalities are present and a liver biopsy has not been conducted. Clinical chemistry criteria for DILI is defined as elevation of the alanine aminotransferase (ALT) or the aspartate aminotransferase (AST) $>5\times$ upper limit of normal (ULN) without symptoms, or rise of alkaline phosphate (ALP) $>2\times$ ULN or rise of bilirubin $>2\times$ ULN with any rise of AST and ALT, or rise of AST or ALT <5 ULN with symptoms [10,11].

If liver injury recovers within 6 months, it is called acute liver injury (ALI), and if it persists for more than 6 months, it is said to be a chronic liver injury. ALI accounts for most cases of DILI and it is divided into hepatocellular, cholestatic, and mixed types based on the R-ratio. The R-ratio is calculated by dividing ALT by ALP, using multiples of ULN for both values. R-ratios of >5 define hepatocellular; <2, cholestatic; and between 2 and 5, a mixed pattern of enzymes [12].

Spectrum of drug-induced liver injury

The DILI spectrum is variable and broad; in most cases, hepatocytes are damaged, but cholangiocytes, stellate cells, and sinusoidal endothelial cells can also be damaged, and several other types of cells can also be damaged simultaneously. DILI can manifest itself as almost any kind of liver disease, from acute hepatitis to chronic hepatitis, fatty liver or steatohepatitis, vascular damage, liver cirrhosis, and even hepatic tumors (Fig. 1) [13,14].

Incidence of drug-induced liver injury

It is reported that the annual incidence of DILI is between 10 and 15 per 10,000 to 100,000 persons [15,16]. However, the actual incidence is estimated to be higher because diagnosis is not easy, and it is often disregarded unintentionally and is therefore not reported in the literature. A prospective study on DILI conducted in Korea estimated that 12 out of every 100,000 persons are admitted to university hospitals per year (data for 2005–2007) [17].

Diagnosis of drug-induced liver injury

1. History taking

The most important factor for the diagnosis of DILI is careful history taking because DILI is a diagnosis of exclusion. The history of drug administration and the onset and progression of liver biochemical abnormalities must be accurate.

2. Roussel Uclaf Causality Assessment Method

The Roussel Uclaf Causality Assessment Method (RUCAM) is a diagnostic tool that makes a probabilistic decision using a scorecard divided into 7 categories. The total scores ranges from less than 0 to 14, and the final score is interpreted as follows: highly probable (>8), probable (6–8), possible (3–5), unlikely (1–2), or excluded (<0) (Table 1) [18]. Currently, scores are conveniently calculated using the website (http://www.pmidcalc.org/?sid=8229110&newtest=Y). Further, RUCAM can be easily used in clinical fields; however, in the case of liver transplantation for hepatic failure and HDS hepatotoxicity caused by Chinese medicine, health food, and folk remedies, the RUCAM scores may be low. In addition, the reproducibility of scoring is low [19].

3. Drug-Induced Liver Injury Network expert opinion

DILIN is a network of US experts who have been conducting DILI-related research since 2004 [20]. The probability of DILI is divided into 5 categories: definite (95% or more), high likely (75%–95%), probable (50%–74%), possibly (25%–49%), and unlikely (25% or less) (Table 2) [21]. Three DILIN experts take a decision based on data recorded for more than 6 months. There is a limitation where only DILIN experts can make decisions; however, there is a high reproducibility advantage over the RUCAM scoring.

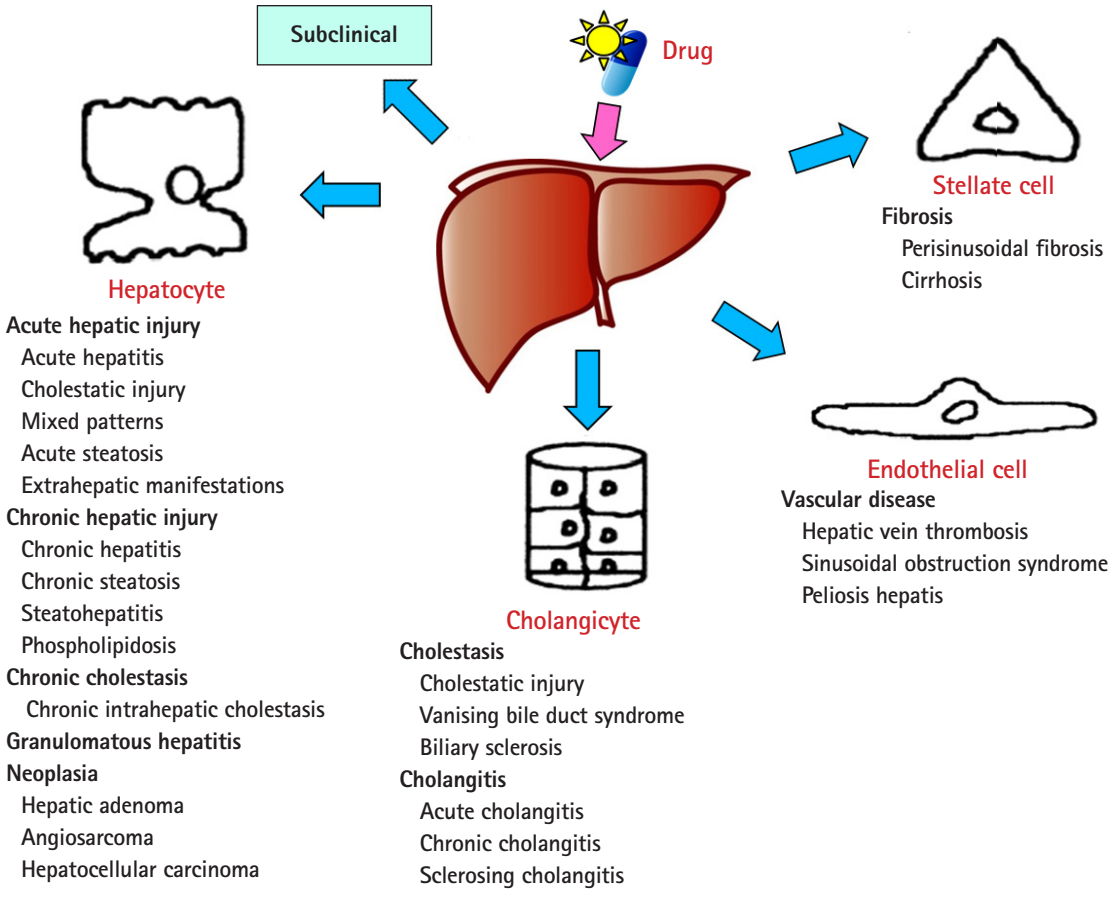

Fig. 1. Spectrum of drug-induced liver injury. The spectrum of drug-induced liver injury is variable and broad from asymptomatic to liver failure. Drugs can damage not only hepatocytes but also cholangiocytes, stellate cells, sinusoidal endothelial cells, and they can cause acute hepatitis, chronic hepatitis, granulomatous hepatitis, neoplasia, cholestasis, cholangitis, vascular disease, and fibrosis.

Table 1. Roussel Uclaf Causality Assessment Method scale

Category	Score	Likelihood (%)	Description
Highly probable	>8	>75	Highly probable, including "highly likely" and "definite." The evidence for the drug causing the injury is beyond a reasonable doubt, clear, and convincing
Probable	6–8	50–74	The preponderance of the evidence supports the link between the drug and the liver injury
Possible	3–5	25–49	The evidence for the drug causing the injury is equivocal but present
Unlikely	1–3	<25	There is evidence that an etiological factor other than a drug caused the injury
Excluded	<1	0	Causes could be excluded

Table 2. Drug-induced Liver Injury Network scale

Category	Score	Likelihood (%)	Description
Definite	1	>95	The evidence for the drug causing the injury is beyond a reasonable doubt
Highly likely	2	75–95	The evidence for the drug causing the injury is clear and convincing but not definite
Probable	3	50–74	The preponderance of the evidence supports the link between the drug and the liver injury
Possible	4	25–49	The evidence for the drug causing the injury is equivocal but present
Unlikely	5	<25	There is evidence that an etiological factor other than a drug caused the injury
Not applicable	0	0	Key elements of the drug exposure history, initial presentation, alternative diagnoses, and/or diagnostic evaluation prevent one from determining a causality score

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4. Liver biopsy

Although there are no characteristic pathological indicators for DILI, sometimes characteristic pathological findings based on the drug may appear, and this can help identify other liver diseases and the severity of liver injury. According to the ACG guideline, a liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated. Moreover, a liver biopsy may be considered if the liver biochemistries continues to increase or the liver function deteriorates despite the interruption of a suspected drug; if the peak ALT level has not dropped by > 50% at 30–60 days after onset in cases of hepatocellular DILI; if the peak ALP level has not dropped by > 50% at 180 days in the cases of cholestatic DILI despite stopping the suspected offending agent; in cases of DILI where continued use or re-exposure to the implicated agent is expected; or if liver biochemistry abnormalities persist beyond 180 days in the evaluation for the presence of chronic liver diseases and chronic DILI [7].

5. Biomarkers

Recently, there has been a growing interest in finding biomarkers that predict the occurrence of DILI, accurately diagnose it, and predict a poor prognosis. Biomarker candidates such as glutamate dehydrogenase, high-mobility group box 1, and keratin-18 have been found [22], and DILI studies using micro-ribonucleic acid, high throughput proteomics, genomics, and metabolomics have been attempted [23,24].

Mechanisms of drug-induced liver injury

Traditionally, DILI has been reported to be caused by intrinsic and idiosyncratic reactions, and sometimes, both may occur together. Intrinsic liver injury is dose dependent and predictable. On the other hand, idiosyncratic liver injury is divided into immunoallergic and metabolic idiosyncratic reactions regardless of dose, and it is unpredictable.

However, Lammert et al. [25] reported the relationship between the daily dose of oral medications and idiosyncratic DILI. Higher daily doses (> 50 mg/day) were associated with serious hepatic events such as liver failure, liver transplantation, and death, but there was no association with lower daily doses (< 10 mg). Thus, dosage also appears to play a role in idiosyncratic liver injury. The traditional mechanism identified only the upstream of the mechanism of intrinsic and idiosyncratic reactions that cause liver injury. The current concepts of mechanisms in DILI focused not only on the upstream but also on the downstream. In other words, the hepatocyte injury mechanism is divided into 3 stages: hepatocyte injury (first stage), mitochondria permeability transition (second stage) belonging to downstream, and hepatocyte death (last stage) (Fig. 2) [26]. The initial hepatocyte injury caused by the drug does not uniformly progress to the third stage, but the injured hepatocyte may be recovered with the defense and regeneration ability of the patient. In addition, various environmental and genetic factors are involved in each stage, and the degree of individual liver injury is different.

In addition to hepatocellular injury caused by drugs, drug-induced cholestasis is also important (Fig. 3). There are 3 triggering factors that induce cholestasis, including effects on drug transporters, various hepatocellular changes, and altered bile canaliculi dynamics [27]. The function of membrane drug transporters involved is inhibited, resulting in cholestasis. In addition, the drug metabolite that exits through the canalicular membrane damages the cholangiocyte, causing cholestasis. Liver injury may be exacerbated as the accumulation of drugs in the liver via enterohepatic circulation or cholehepatic shunt.

In addition, liver injury may be further exacerbated by transmitting hepatic injury and inflammatory signals to neighboring cells through other gap junctions, and the liver injury may be targeted to non-parenchymal cells other than hepatocytes and cholangiocytes [28].

Individual differences in drug-induced liver injury

Some people suffer liver injuries and others do not because every individual has different susceptibility to drugs. The risk factors for DILI can be divided into genetic factors and environmental factors [29,30]. Genetic factors include mutations in the cytochromes P450 enzyme, the expression of transport proteins and nuclear receptors, and changes in the levels of immune components. Environmental factors include old age, female gender, drug combination, previous drug adverse reactions, nutritional status, pregnancy, alcohol consumption, inflammation, and existing diseases (Table 3). The important fact is that the different risk factors are involved in different three-step model concepts that describe the changed liver injury mechanism. Changes in gut microbiota affect the drug metabolism and immune system, and it is interesting that it is one of the risk factors of DILI [31].

Drug-induced liver injury in patients with pre-existing liver disease

There is much debate over whether DILI occurs more frequently in patients with pre-existing liver diseases than in normal people.

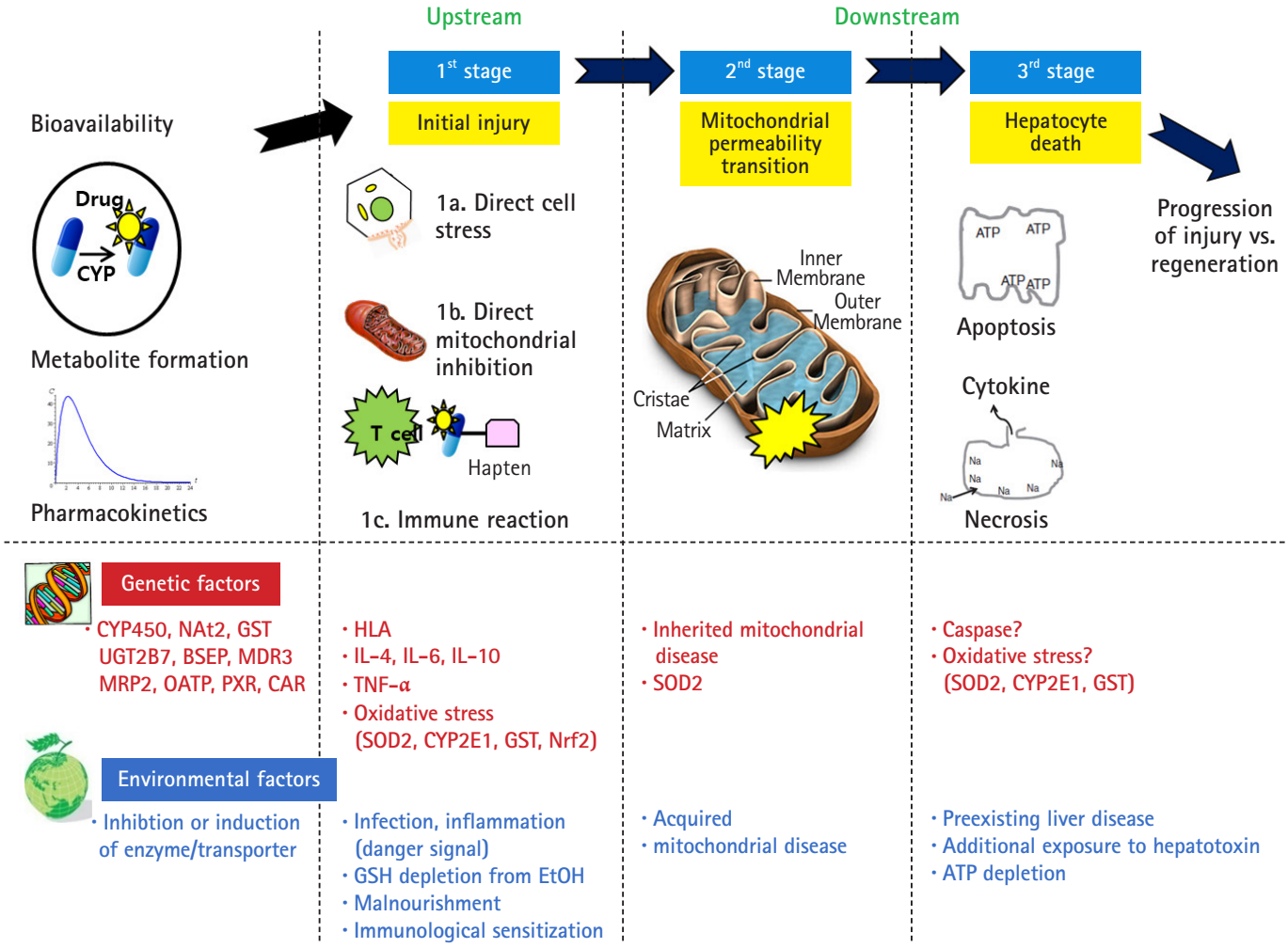

Fig. 2. Mechanism of drug-induced liver injury. The hepatocyte injury mechanism is divided into three stages: (1) first stage (initial hepatocellular injury); initial injury is exerted through direct cell stress, direct mitochondrial inhibition, and/or specific immune reactions; (2) second stage (mitochondrial permeability transition); initial injury can lead to MPT. Direct cell stress causes MPT via the intrinsic pathway, and (3) final stage (hepatocyte death); MPT leads to necrosis or apoptosis depending on the availability of ATP, which is not uniformly progressive from the initial hepatocyte injury to the third stage, and damaged hepatocytes can be recovered depending on their defense and regeneration ability. Various environmental factors and genetic factors are involved in each step, and the degree of individual liver injury is different. MTP, mitochondrial permeability transition; ATP, adenosine triphosphate; CYP, cytochrome P450; NAt2, N-acetyltransferase 2; GST, glutathione S-transferase; UGT2B7, glycosyltransferase 2B7; BSEP, bile salt export pump; MDR3, multidrug resistance protein 3; MRP2, multidrug resistance-associated protein 2; OATP, organic-anion-transporting polypeptide; PXR, pregnane X receptor; CAR, constitutive androstane receptor; HLA, human leukocyte antigen; IL, interleukin; TNR-α, tumor necrosis factor-alpha; SOD2, superoxide dismutase 2; Nrf2, nuclear factor erythroid 2-related factor 2; GSH, glutathione S-transferase; EtOH, ethanol.

There are several exceptions, but they are not more frequent. However, it is known that DILI is more critical and has a higher mortality rate in patients with pre-existing liver diseases [32,33].

Predictive model of progression to acute liver failure

DILI is usually reversible and considered benign; however, it sometimes progresses to hepatic failure, requiring liver transplantation or causing death. According to Hyman Zimmerman's Hy's law, the hepatocellular type of DILI is known to have a mortality rate of over 10% if accompanied by jaundice [34,35]. Hy's law is known to have a high specificity (0.92) but a low sensitivity (0.68) for the prediction of acute liver failure (ALF) [36].

A new index predicting ALF in DILI has been recently proposed by Robles-Diaz et al. [37], which integrates Hy's law with the new R-ratio (nR) and demonstrates a sensitivity of 90% and a specificity of 63%. The nR is calculated as (the highest AST or

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Table 3. Risk factors of drug-induced liver injury

Genetic factor	Environmental factor
Phase 1 enzymes	Age
CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1	Sex
Phase 2 enzymes	Race
NAT2, GSTM1, GSTT1, UGT2B7	Drug interaction
Phase 3 transporters	Alcohol
BSEP, MRP2, MDR3	Inflammation
Phase 0 transporter	Underlying disease
OATP	
Nuclear receptors	Pre-existing liver disease
PXR, CAR	HIV
Immunologic	Diabetes
HLA class antigen	
Cytokines	Pregnancy
IL-4, IL-10, TNF-α	Nutrition
Mitochondrial mutation	Previous history
DNA mutations (POLG), MnSOD	
Epigenetics	

CYP, cytochrome P450; NAT2, N-acetyltransferase 2; GST, glutathione S-transferase; UGT2B7, glycosyltransferase 2B7; BSEP, bile salt export pump; MRP2, multidrug resistance-associated protein 2; MDR3, multidrug resistance protein 3; OATP, organic-anion-transporting polypeptide; PXR, pregnane X receptor; CAR, constitutive androstane receptor; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IL, interleukin; TNR-α, tumor necrosis factor-alpha; DNA, deoxyribonucleic acid; POLG, polymerase gamma; MnSOD, manganese-dependent superoxide dismutase.

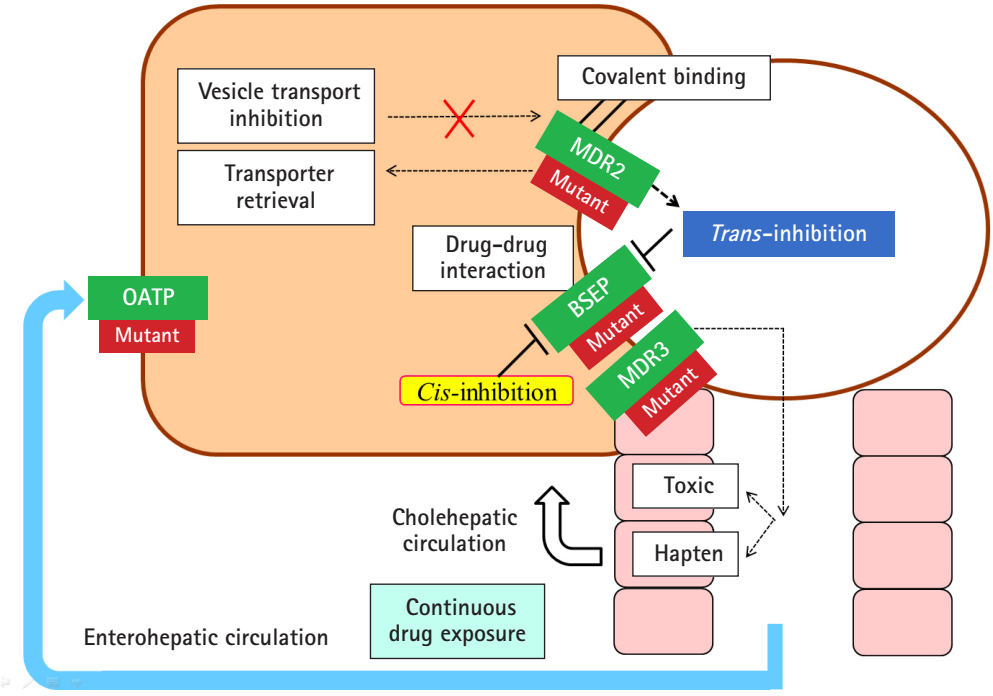

Fig. 3. Different mechanism of drug-induced cholestasis. Drug-induced cholestasis is caused by the degradation of the expression and function of the transport protein due to the environmental factors that directly inhibit the function of the transport protein and the genetic variation of the transport protein. In addition, the drug metabolite that exits through the canalicular membrane damages cholangiocyte, causing cholestasis. A liver injury may be exacerbated by drug accumulation in the liver via drug reabsorption through enterohepatic or cholehepatic circulation. Directly inhibtion of BSEP function is cis-inhibtion, whereas indirectly inhibition of BSEP function from the canalicular lumen is trans-inhibtion. OATP, organic-anion-transporting polypeptide; MRP2, multidrug resistance-associated protein 2; BSEP, bile salt export pump; MDR3, multidrug resistance protein 3.

ALT/ULN)/(ALP/ULN); AST is substituted for ALT, if the AST yields a greater R-ratio.

Recently, a drug-induced liver toxicity ALF score (DrILTox ALF Score) was developed to predict the progression of liver failure in DILI [36]. Scoring is based on platelet counts and total bilirubin (TB) [DrILTox ALF Score = −0.00691292 × platelet count +0.19091500 × TB (per mg/dL)]. Although the specificity (0.76) was slightly lower, the sensitivity (0.91) was higher than those of Hy's law criteria. The risk of liver failure becomes higher as the platelet count decreases and TB increases.

Herbal and dietary supplement hepatotoxicity

HDS include herbs or other plant materials, vitamins, and minerals. The incidence of HDS hepatotoxicity is increasing compared to that in the past [38]. In general, it is estimated that HDS hepatotoxicity is actually more likely to occur because it is not easy to diagnose, it is often missed if the symptoms are overlooked, and often, the cases are not reported in the literature in addition to inadequate treatment for the patient. It is difficult to detect the toxic substances contained in the herb itself, unlike the commercial medicines whose causative substances are clearly defined, and it is difficult to prove causal relationships between the herb-specific components and the liver injury. Since the herb is a mixture of various substances, it is difficult to know which ingredient causes the liver injury. It can be contaminated with microorganisms or fungi during distribution or storage, or the liver injury may be caused by herb denaturation. It should be noted that there may also be liver injury caused by impurities, heavy metal contamination, or illegal incorporation of drugs into the herb (Fig. 4).

Similar to that for the liver injury caused by commercial drugs, RUCAM scoring is applied to diagnose HDS hepatotoxicity. However, it is necessary to adjust the RUCAM for HDS hepatotoxicity [39,40] because there are few reports of HDS hepatotoxicity, and thus, the results tend to be lower than the actual RUCAM scores; further, the time between the termination of herb administration and symptom development is often long as low concentrations of plants are often taken over a long period of time.

Interestingly, Suh et al. [41] showed that psychological factors that present vulnerability to the temptation to use alternative medicines such as herbs and plant preparations are important for understanding toxic liver injury. Therefore, the treatment of toxic liver injury itself is important. However, to prevent toxic liver injury and recurrence, it is necessary to implement an active strategy to understand and improve anxiety and depression faced by the patient.

Treatment of drug-induced liver injury

Stopping the suspected drugs is key to treatment. Other treatments involve the administration of N-acetyl cysteine (NAC) and steroids, and liver transplantation are considered when hepatic failure occurs.

1. Stopping the suspected drug

Follow-ups are necessary after stopping not only the suspected drug but also herbal medicines, plant preparations, and health food. Depending on when the drug is discontinued, the severity of the liver injury can vary; therefore, the drug should be stopped as early as possible. Since such liver injuries are reversible to normal state, it is necessary to repeat liver function tests after stopping the medication. In some cases, even if the drug is discontinued, it may not immediately improve the liver condition and the liver injury may continue; therefore, careful follow-ups must be performed. It is very difficult to assess if the drug should be continued if there is a rise in hepatic enzymes in the liver function test during the course of the treatment. Further, if the suspected causative drug is important for the control of the underlying disease, the balance between the risk of progression of the underlying disease after drug withdrawal and the risk of exacerbation of liver damage due to the continued administration of potentially related drugs should be considered. According to the "stop rule" for new drugs developed by the US Food and Drug Administration (FDA) [42], the guidelines are based on AST, ALT, and TB, and the medication being administered should be immediately stopped when any of the following results are obtained: (1) ALT or AST > 8 × ULN; (2) ALT or AST remains > 5 × ULN over 2 weeks; (3) ALT or AST > 3 × ULN & TB > 2 × ULN or international normalized ratio (INR) > 1.5; (4) ALT or AST > 3 × ULN with symptoms (e.g., fatigue, nausea and vomiting, right upper quadrant pain, fever, and rash) or eosinophilia. Therefore, it is acceptable to follow the FDA "stop rule" in clinical practice.

2. Specific treatment

Although no specific therapies are available for DILI, NAC (IV infusion, 50–150 mg/kg/day) may be administered for at least 3 days in patients with early or sub-ALF [43-45]; it is not recommended for children with severe DILI as it can lead to ALF. Several studies have shown that steroids can prove effective; however, there have been some debates on the efficacy of corticosteroid in treating patients with DILI [46,47]. In the case of immunoallergic or autoimmune hepatitis-like DILI, the administration of glucocorticoid may be considered.

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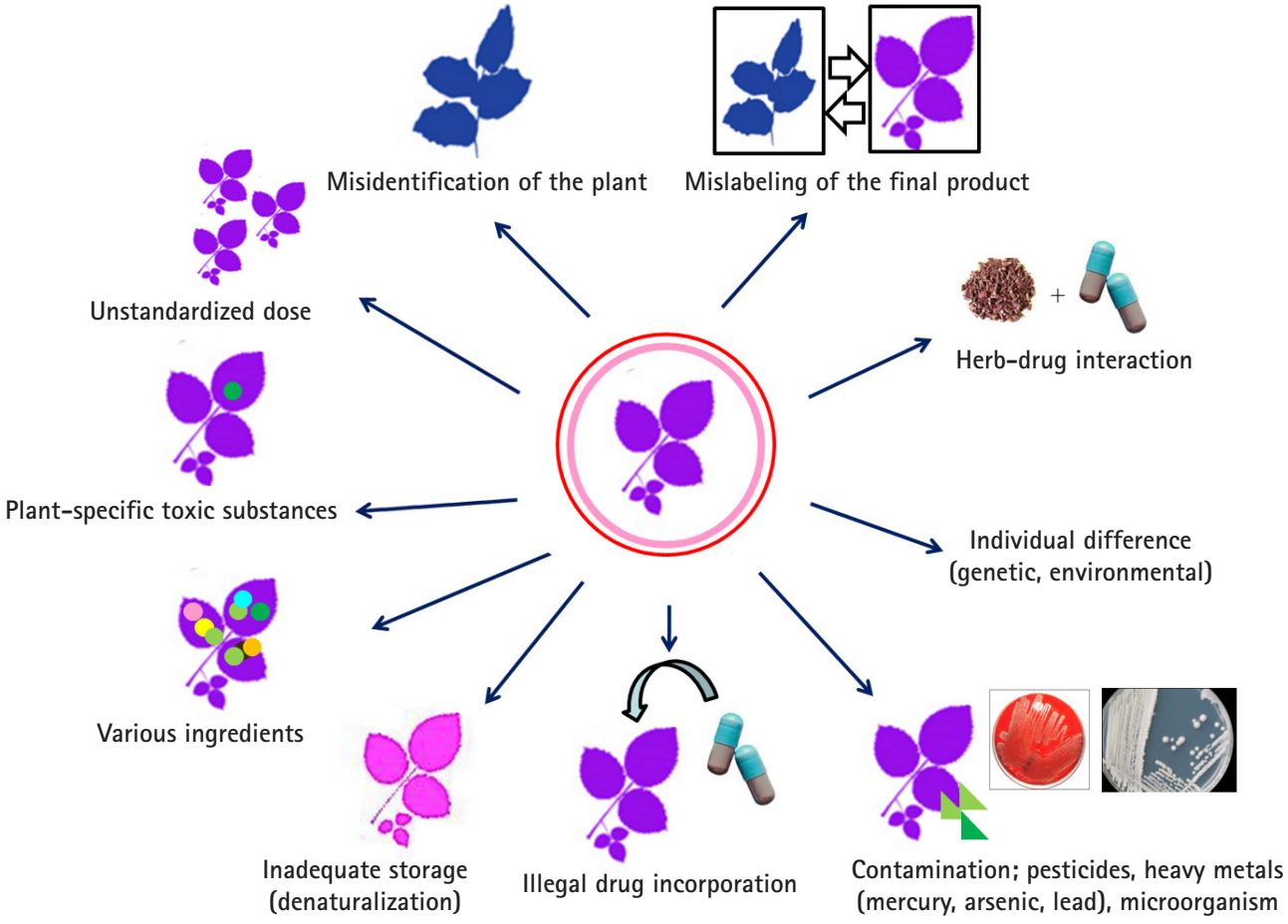

Fig. 4. Risk factors contributing to hepatotoxicity of herbal remedies. There are many causative factors for herb-induced liver injury such as the misidentification of the plant, mislabeling of the final product, unstandardized dose, plant-specific toxic substances, various ingredients, denaturalization during inadequate storage, illegal drug incorporation, contamination of the plant by various chemicals, heavy metals, microorganisms, individual difference due to genetic or environmental factors, and herb-drug interactions.

3. Re-administration of suspected drugs

Although there is controversy regarding the unconditional re-administration of all suspected drugs that cause DILI, care should be taken because re-administration of immunoallergic reacting drugs may cause more serious liver damage than before.

4. Liver transplantation

Liver transplantation should be considered if the liver function deteriorates and is concomitant with coagulopathy and encephalopathy [48]. Survival is less than 20% if liver transplantation is not performed in drug-induced ALF caused by a hypersensitivity reaction. The recommendations of Kings' College on indications for liver transplantation due to drug-induced liver failure as follows: In case of acetaminophen-induced liver failure, liver transplantation is required when the arterial blood pH is < 7.3, regardless of encephalopathy grade, or if grade III or IV encephalopathy and an INR > 6.5 and a serum creatinine > 3.4 mg/dL. Liver transplantation is required for liver failure caused by non-acetaminophen drugs as follows: patients with prothrombin time (PT) > 100 s (INR > 6.5) (with or without encephalopathy, regardless of grade) or who satisfy any 3 of the following criteria: (1) age < 10 or > 40 years of age; (2) etiology: non-A/non-B hepatitis, drug-induced; (3) duration of jaundice to hepatic encephalopathy > 7 days; (4) PT > 50 s (INR > 3.5); or (5) serum bilirubin level > 17 mg/dL (> 300 μmol/dL) [49,50].

5. New treatments for drug-induced liver injury

Many studies have been actively pursued to develop therapeutic agents aimed at nuclear receptors in DILI [51,52]. The activation of constitutive androstane receptor (CAR) and pregnane X receptor (PXR) exacerbates hepatotoxicity by acetaminophen [53,54]. Thus, compounds that inhibit CAR and PXR may be beneficial

for the treatment of hepatic damage induced by acetaminophen. Farnesoid X receptor (FXR) plays an important role in the regulation of bile acid synthesis and metabolism. Thus, FXR agonists such as obeticholic acid have been considered as promising targets for the treatment of cholestatic disorders involving drug-induced cholestasis.

Autophagy refers to the activity in which a cell obtains energy by dissolving its protein or removing unnecessary cell components when it becomes nutrient deficient. Recently, studies on autophagy have been actively conducted in various areas such as cancer, diabetes, infectious diseases, and Crohn's disease. For DILI, a new therapeutic approach is being attempted to reduce the liver injury by controlling autophagy [55]. Acetaminophen overdose results in hepatic necrosis caused by mitochondrial damage. The activation of autophagy degrades the damaged cytoplasmic proteins, which allows cells to survive without cell necrosis. While liver injury is prevented by the administration of rapamycin (autophagy inducer), 3-methyladenine, or chloroquine (autophagy inhibitor), they have been shown to decrease liver injury. Further, it is expected that several new treatments, including autophagy induction, will be developed and applied to the treatment of DILI in clinical practice.

Drug-induced liver injury and the fourth industrial revolution

DILI has also been actively researched by applying various new technologies of the fourth industrial revolution. Recently, organ-on-a-chip (OOC) such as liver, lung, heart, nerve, and skin have been developed [56,57]. OOC is a technique that imitates the mechanical and physiological cellular responses as well as the functions and characteristics of the organs by culturing cells that constitute a living OOC on which electronic circuits are placed. The OOC is worth using as a model for drug development and toxicity assessment. A liver-on-a-chip can be used to evaluate the toxicity of a drug without animal testing [58]. In addition, it is reported that deep learning using artificial intelligence can predict the occurrence of DILI [59]. It is expected that research using various technologies of the fourth industrial revolution will help predict the side effects and drug–drug interactions in advance through "In-Silico," a computer virtual test using biological big data [60,61].

Conclusion

DILI is a problem that can be encountered in clinical settings, and clinicians should therefore have appropriate knowledge and diagnosis and treatment skills. We hope that various biomarkers to accurately diagnose and predict the prognosis of DILI will be developed and used conveniently, and various new technologies of the fourth industrial revolution will be developed and applied to DILI.

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Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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