Chapter 13
DLI Induced by Herbal Medicine: What Are the Characteristics of DLI due to Herbal Medicines?

Mitsuhiro Abe, Kenji Tsushima, and Koichiro Tatsumi

Abstract In many countries, herbal medicine has been developed and is currently practiced. Herbal medicine involves the use of the stalks, roots, leaves, flowers, and berries of several different plant species for medical treatment. Many practitioners believe that herbal medication has no side effects because of its natural origin. Thus, herbal medication has been used for a long time with little awareness of its side effects. However, there is an increasing incidence of interstitial pneumonia due to a drug-induced lung injury (DLI), which could be induced by common drugs. Moreover, increasing cases of bronchiolitis obliterans and pulmonary hypertension are being reported; further, these are drug-induced conditions. Clinicians should be more aware of DLI symptoms caused by herbal medication and interrogate patients regarding their use of herbal medication and supplements as well as prescription drugs.

Keywords Herbal medicine • Drug-induced lung injury (DLI) • Shosaikoto (SST)

13.1 Introduction

Generally, herbs are plants that are used for flavoring food and drugs. Broadly, "herbs" can be the leaves, roots, flowers, seeds, resin, bark, berries, or other segments of a plant. Some herbs have strong side effects and are toxic in large doses. "Herbal medicine" involves the use of herbs for medical treatment. Herbal medicine has a long tradition that has evolved independently over many years in different regions worldwide.

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Since the nineteenth century, the bioactive components of herbs used in herbal medicine have been identified and extracted to synthesize a drug formulation. In the twentieth century, evidence-based medical research to evaluate the effects of drugs in large clinical trials has become mainstream. Along with this development, the practice of conventional herbal medicine has decreased.

However, recently, the use of herbal medication to treat certain diseases has been increasing. For example, herbal medicine is being used increasingly to augment the efficacy of chemotherapy and reduce toxicity [1], extend the survival of patients with uterine cervical cancer [2], and reduce postoperative ileus [3].

Many herbs are not readily identified as medication. People can obtain these herbs without visiting a clinic or hospital. Therefore, it is difficult to accurately recognize the market size and side effects of herbal medicine.

Typically, herbal medication is considered a probable cause of adverse events [4]. For example, aconitum (monkshood), which is often used in Chinese herbal medicine, is highly toxic (lethal dose, 0.2–1 g). Aconitum is usually heat-detoxified. Many other herbal drug formulations also have some toxic properties.

As the practice of herbal medicine increases, side effects are being increasingly reported. In this regard, the consumption of healthy and natural foods is just as important as the ingestion of prescription drugs in influencing patient health. To diagnose side effects accurately, we should always consider these side effects. Moreover, we should ask patients sufficiently and understand the characteristics of DLI in each drug.

13.2 Diagnosis of DLI Related to Herbal Medication

There is no special method to diagnose a DLI associated with the use of herbal medication. The Japanese Respiratory Society has proposed five diagnostic criteria for a DLI [4] (Table 13.1): (1) a patient history of ingestion of a drug that induces a lung injury, (2) the clinical manifestations reported as drug-induced lung injury, (3) other causes of the clinical manifestations are excluded, (4) the clinical manifestations improve after drug discontinuation, and (5) the exacerbation of the clinical manifestations after resuming drug administration. Resuming drug administration to identify the causative drug is usually not recommended; however, it is acceptable if the patient requires the drug, and a reasonable level of safety is assured.

The drug lymphocyte stimulation test (DLST) is sometimes helpful in the diagnosis of a DLI. ^{3}H-thymidine uptake by lymphocytes is measured as a stimulating index. The DLST has a positivity rate of 66.9% in patients with drug-induced pneumonia [4, 5]. The rate of drug-induced pneumonia due to herbal medication is 67.6% [5]. However, the results of the DLST should be interpreted with caution for several reasons. First, the DLST is performed in vitro; therefore, the results may be inconsistent with the in vivo condition. Second, the administration procedure is not well established; therefore, the results of the DLST can be different at different institutions.

Table 13.1 Diagnostic criteria for DLIs [4]

1.	History of ingestion of a drug that is known to induce lung injury	Specifically inquire about the following when taking the patient's history: over-the-counter (OTC) drugs, health foods, and illegal narcotic drugs/antihypnotic drugs
2.	The clinical manifestations have been reported to be induced by a drug	The clinical manifestations include clinical findings, imaging findings, and pathological features
3.	Other causes of the clinical manifestations could be ruled out	Differentiation from infection, cardiogenic pulmonary edema, exacerbation of an underlying disease, etc.
4.	Improvement of the clinical manifestations after drug discontinuation	Spontaneous remission or remission in response to an adrenocorticosteroid
5.	Exacerbation of the clinical manifestations after resuming drug administration	Resuming drug administration to identify if the causative drug is not generally recommended but is acceptable if the patient requires the drug and safety is assured

Third, false-positive or false-negative reactions often occur when the DLST is used as a diagnostic test for a DLI, regardless of whether herbal medication is involved. Moreover, herbal medicine includes several plant components (Table 13.2). Some of these components cannot be absorbed in the intestine. A DLST test is performed in vitro; therefore, the component that is not present in the blood in vivo can react with the lymphocytes in vitro (i.e., a false-positive result). For example, Sho-Saiko-To (SST) can directly stimulate lymphocytes, thereby resulting in a false-positive result [4, 6]. Nakayama reported that a DLST for SST was positive in 27.5% of healthy controls [6]. Therefore, we need to carefully consider the result of a DLST in patients suspected with a DLI due to herbal medication.

13.3 DLI due to Herbal Medication

13.3.1 Characteristics of a DLI due to Herbal Medication

Generally, any unfavorable medical occurrence in a patient or a subject of clinical investigation administered a pharmaceutical product is referred to as an adverse event (AE). A DLI is an AE that occurs specifically in the pulmonary system [7]. A DLI can be classified into several different types based on clinicoradiological features such as the clinical course, laboratory findings, and radiological findings (Table 13.3) [4]. Several pathognomonic findings of a DLI have been reported in patients administered with herbal medication.

The most common pathognomonic of a DLI due to herbal medication is interstitial pneumonia. However, recently, other symptoms such as bronchiolitis obliterans and pulmonary arterial hypertension have been associated with herbal medication-related DLI [8, 9].

Table 13.2 The list of components of herbal medicines in Japan that has been reported to cause drug-induced IP

	bakumondoto	bofutsushosan	boiogito	daikenchuto	daisaikoto	gorinsan	goshajinkigan	hangeshashinto	hochuekkito	junchoto	keigairenngyoto
baimo											
bakumondo	○										
biwayou											
boi			○								
bofu		○									○
bosho		○									
botampi							○				
borei											
bukuryo						○	○				
bushi							○				
byakugo											
byakujutu		○									
byakushi											○
chikujo											
chimo											
chimpi									○		
chotoko											
daio					○					○	
gomin											
goshitsu							○				
hakka											○
hange	○				○			○			
ireisen											
jikoppi											
jio						○	○			○	○

kankyo				○				○			
karokon											
kasseki						○					
kanzo	○		○			○		○	○	○	○
keigai											○
keihi							○				
kikyou											○
kijitsu					○					○	○
kobei	○										
kobushi											
koboku										○	
kujin											
kyokatsu											
kyonin										○	
mao		○									
mashin										○	
mokutsu						○					
ninjin	○			○				○	○		
obaku											○
ogi			○						○		
ogon		○			○	○		○		○	○
oren								○			○
renniku											
rengyo											○
ryukotsu											

(continued)

Table 13.2 (continued)

	bakumondoto	bofutsushosan	boiogito	daikenchuto	daisaikoto	gorinsan	goshajinkigan	hangeshashinto	hochuekkito	junchoto	keigairenngyoto
ryutan											
saiko					○				○		○
saishin											
sanshishi						○					○
sansho				○							
sanshuyu							○				
sanyaku							○				
sekko		○									
senkyu											○
shakuyaku					○	○					○
shazenshi						○	○				
shishi											
shokyo			○		○				○		
shoma									○		
sohakuhi											
sojutsu			○						○		
soyo											
takusha						○	○				
taiso	○		○		○			○	○		
temmondo											
tennansho											
toki						○			○	○	○
tonin										○	

	nijutsuto	otsujito	orengedokuto	ryutanshakanto	saibokuto	saikokaryukotsuboreito	saikokeisikannkyoto	saikokeishito	sammotsuogonto
baimo									
bakumondo									
biwayou									
boi									
bofu				△					
bosho									
botampi									
borei						○	○		
bukuryo	○				○	○			
bushi									
byakugo									
byakujutu	○								
byakushi									
chikujo									
chimo									
chimpi	○								
chotoko									
daio		○				△			
gomin									
goshitsu									
hakka				△					
hange	○				○	○		○	
ireisen	○								
jikoppi									
jio				○					○

(continued)

Table 13.2 (continued)

	nijutsuto	otsujito	orengedokuto	ryutanshakanto	saibokuto	saikokaryukotsuboreito	saikokeisikannkyoto	saikokeishito	sammotsuogonto
kankyo							○		
karokon							○		
kasseki									
kanzo	○	○		○	○		○	○	
keigai									
keihi						○	○	○	
kikyou									
kijitsu									
kobei									
kobushi	○								
koboku					○				
kujin									○
kyokatsu	○								
kyonin									
mao									
mashin									
mokutsu				○					
ninjin					○	○		○	
obaku			○	△					
ogi									
ogon	○	○	○	○	○	○	○	○	○
oren			○	△					
renniku									
rengyo				△					
ryukotsu						○			

ryutan				○					
saiko		○			○	○	○	○	
saishin									
sanshishi			○	○					
sansho									
sanshuyu									
sanyaku									
sekko									
senkyu				△					
shakuyaku				△				○	
shazenshi				○					
shishi									
shokyo	○				○	○		○	
shoma		○							
sohakuhi									
sojutsu	○								
soyo					○				
takusha				○					
taiso					○	○		○	
temmondo									
tennansho	○								
toki		○		○					
tonin									

(continued)

Table 13.2 (continued)

	sanoshashinto	seihaito	seishinrenshiin	shakuyakukanzoto	shin'iseihaito	shosaikoto	shoseiryuto	unseiin	yokukansan
baimo		○							
bakumondo		○	○		○				
biwayou					○				
boi									
bofu									
bosho									
botampi									
borei									
bukuryo		○	○						○
bushi									
byakugo					○				
byakujutu									
byakushi									
chikujo		○							
chimo					○				
chimpi		○							
chotoko									○
daio	○								
gomin		○					○		
goshitsu									
hakka									
hange						○	○		
ireisen									
jikoppi			○						
jio								○	

kankyo							○		
karokon									
kasseki									
kanzo		○	○	○		○	○		○
keigai									
keihi							○		
kikyou		○							
kijitsu									
kobei									
kobushi									
koboku									
kujin									
kyokatsu									
kyonin		○							
mao							○		
mashin									
mokutsu									
ninjin			○			○			
obaku								○	
ogi			○						
ogon	○	○	○		○	○		○	
oren	○							○	
renniku			○						
rengyo									
ryukotsu									

(continued)

Table 13.2 (continued)

	sanoshashinto	seihaito	seishinrenshiin	shakuyakukanzoto	shin'iseihaito	shosaikoto	shoseiryuto	unseiin	yokukansan
ryutan									
saiko						○			○
saishin							○		
sanshishi					○			○	
sansho									
sanshuyu									
sanyaku									
sekko					○				
senkyu								○	○
shakuyaku				○			○	○	
shazenshi			○						
shishi		○			○				
shokyo		○				○			
shoma					○				
sohakuhi		○							
sojutsu									○
soyo									
takusha									
taiso		○				○			
temmondo		○							
tennansho									
toki		○						○	○
tonin									

○ always including, △ sometimes including

Table 13.3 Main clinical types and histological diagnoses of DLIs (in contrast to common diffuse pulmonary diseases)

Main lesion site	Clinical disease type	Histological diagnosis
1. Alveolar and interstitial regions	Acute respiratory distress syndrome (ARDS)	Diffuse alveolar damage (DAD)
	Idiopathic interstitial pneumonias (IIPs)	
	Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
	Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
	Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
	Eosinophilic pneumonia (EP)	Eosinophilic pneumonia (EP)
	Hypersensitivity pneumonia (HP)	Hypersensitivity pneumonia (HP)
	Granulomatous interstitial lung diseases	Granulomatous interstitial pneumonia
	Pulmonary edema	Pulmonary edema
	Capillary leak syndrome	Pulmonary edema
	Pulmonary alveolar proteinosis	Alveolar proteinosis
	Diffuse alveolar hemorrhage	Alveolar hemorrhage
	Bronchial asthma	Bronchial asthma
2. Airway	Bronchiolitis obliterans syndrome (BOS)	Bronchiolitis obliterans (BO)
	Pulmonary artery embolism	Pulmonary artery embolism
3. Blood vessels	Vasculitis	Vasculitis
	Pulmonary hypertension	Pulmonary hypertension
	Pulmonary veno-occlusive disease	Pulmonary veno-occlusive disease
4. Pleura	Pleuritis	Pleuritis

In Japan, approximately 140 types of herbal drug formulations have been covered by insurance. Many herbal medicines that are used to treat chronic diseases are sometimes ineffective. Nonetheless, herbal medication has been generally considered an unlikely cause of adverse reactions [4]. The first case of interstitial pneumonia due to herbal medication was reported in 1989 [10]. This patient was administered Sho-Saiko-To (SST) for treatment of chronic hepatitis. Thereafter, interstitial pneumonia has been diagnosed in an increasing number of patients receiving herbal medication.

13.3.2 Interstitial Pneumonia (IP)

Drug-induced IP is the most common characteristic of a DLI and is classified into two types: cytotoxic and allergic drug-induced IP [11].

Cytotoxic drug-induced IP involves multiple mechanisms, including reactive oxygen species (ROS) synthesis, decreased deactivation of metabolites in the lung, impaired alveolar-repair mechanisms, and release of various cytokines [12]. Additionally, cytotoxic drug-induced IP shows a diffuse alveolar damage (DAD) pattern and often presents as a severe clinical manifestation with a lethal outcome. Chemotherapeutic agents, antirheumatic drugs, and amiodarone are typical agents that cause cytotoxic drug-induced IP. However, cytotoxic drug-induced IP due to herbal medication has not been reported. Cases of allergic drug-induced IP often improve with corticosteroid treatment. However, some cases of allergic drug-induced IP have resulted in deaths; therefore, some of these cases may involve conditions other than allergic drug-induced IP.

As mentioned previously, the first report of IP due to herbal medication involved SST in 1989 [10], which occurred in Japan. SST consists of seven types of herbs, saiko (*Bupleurum scorzonerifolium*), ogon (*Scutellaria baicalensis*), hange (*Pinellia ternata*), shokyo (*Zingiber officinale*), taiso (*Ziziphus jujube*), ginseng (*Panax ginseng*), and kanzo (*Glycyrrhiza uralensis*). SST improved liver function in patients with chronic active hepatitis in a double-blind randomized study [13]. Some studies report that only two SST components (ogon and hange) were positive in a DLST [10, 14]. However, another study found that all seven components were positive in a DLST [15]. Shimodaira reported in 2000 that ogon, kanzo, and shokyo are commonly involved in lung injury after a review of 488 patients administered with herbal medication [16].

Since the first report in 1989, the number of reports of drug-induced IP due to SST has increased. More than 100 cases have been reported in 10 years [17]. Ten people with SST-induced IP have died, and this condition has become a serious social problem in Japan. Suzuki reported the clinical characteristics of SST-induced IP (Table 13.4) [17]. The period of onset of SST-induced IP was longer (78.9 ± 121.0 days) than that for non-herbal drug-induced IP. The proportion of SST-induced IP patients that was positive for the hepatitis C virus (HCV) antibody was 75.7%. Laboratory findings indicated high lactic dehydrogenase enzyme (LDH) and C-reactive protein (CRP) levels, hypoxemia, and a high proportion of lymphocytes in the bronchoalveolar lavage fluid. Chest computed tomography (CT) findings indicated that ground-glass opacity was 29.2% and air-space consolidation was 45.8%.

Additionally, Sato characterized patients with SST-induced IP [18]. A comparison of the survivors and non-survivors revealed a significant difference in the prevalence of pulmonary complications such as idiopathic pulmonary fibrosis, duration of treatment after onset, degree of hypoxemia, prevalence of liver cirrhosis, positive proportion of HCV antibody, and CRP values.

Table 13.4 Clinical features of Sho-Saiko-To-induced interstitial pneumonia

Age (years)		64.5 ± 8.2
Male/female		69/31
Underlying disease	Chronic hepatitis	52 (52%)
	Cirrhosis of the liver	29 (29%)
	Liver dysfunction	18 (18%)
	Others	1 (1%)
Period to onset (day)		78.9 ± 121.0 (n = 80)
Duration of administration after the onset (day)		6.9 ± 9.3 (n = 84)
First symptom	Cough	87.6%
	Dyspnea	85.9%
	Fever	79.8%
Laboratory findings	Hematology/serology	
	White blood cell	7823 ± 3324/mm^3 (n = 77)
	Eosinophils	246 ± 288/mm^3 (n = 56)
	LDH	681 ± 310 IU/L (n = 74)
	CRP	5.3 ± 4.9 mg/dL (n = 53)
	Arterial blood gas	
	PaO_2	48.5 ± 13.0 Torr (n = 76)
	$PaCO_2$	33.5 ± 6.3 Torr (n = 71)
	Bronchoalveolar lavage (n = 17)	
	Macrophage	38.0 ± 28.6%
	Lymphocytes	46.2 ± 29.2%
	Neutrophils	12.4 ± 16.6%
	Eosinophils	3.2 ± 3.5%
	CD_4/CD_8 ratio	0.61 ± 0.51%
Radiological findings	Chest X-ray (n = 41)	
	Ground-glass opacity	58.5%
	Infiltration	26.8%
	Ground-glass opacity + infiltration	14.6%
	Chest CT (n = 24)	
	Ground-glass opacity	29.2%
	Air-space consolidation	45.8%
	Ground-glass opacity + air-space consolidation	4.2%
	Nodular shadow	16.7%

LDH lactic dehydrogenase enzyme, *CRP* C-reactive protein, *CT* computed tomography

A delay in the discontinuation of SST administration can result in death. Although the treatment response for allergic drug-induced IP is generally positive, cytotoxic mechanisms may result in death.

Fibroblasts produce inflammatory cytokines (such as IL-1, IL-6, and IL-8) in vitro in response to stimulation by SST, and this reaction is stronger in fibroblasts from the lungs of patients with idiopathic pulmonary fibrosis (IPF) than in healthy

individuals [19]. Furthermore, the proportion of patients with SST-induced IP that were positive for HCV antibody was high. Interferon (IFN) production due to viral infection either may be involved in the onset of drug-induced IP or may increase its severity.

In Japan, SST is frequently reported as the causative agent of an AE involving IP compared to other herbal medicines. An AE that involved IP has been reported for 25 species of herbal medicines, including SST [20]. Some IP patients use multiple herbal medicines, while others develop IP after herbal medicine use was discontinued. We should recognize that all herbal medicines pose a risk for developing drug-induced IP.

13.3.3 Bronchiolitis Obliterans

An outbreak of bronchiolitis obliterans in association with *Sauropus androgynus* (*Sauropus albicans*) was reported in Taiwan in *Lancet* in 1996 [8]. *Sauropus androgynus* (SA) is a plant from the *Euphorbiaceae* family. This plant grows to a height of approximately 1.5 m. The leaves of this plant are eaten as a vegetable particularly in Malaysia, Indonesia, and Vietnam. SA has been imported into Taiwan from these countries since 1982. Some people believe that SA can be used for weight management, especially young and middle-aged women in Southeast Asia who regularly consume SA. The characteristic DLI due to herbal medicine is reported as only IP. Therefore, the 1996 report of bronchiolitis obliterans as a new pathognomonic of a DLI due to SA was of interest of many researchers.

The mean age of the 23 women in this 1996 report by Lai [8] was 39 years (range, 21–52 years). SA is usually cooked in most Southeast Asian countries; however, 23 patients drank juice from uncooked SA. The mean estimated total amount of ingested SA per person was 8–16 kg (range, 2–21 kg) over a mean of approximately 10 weeks (range, 2–13 weeks). Table 13.5 shows the clinical features of SA-induced bronchiolitis obliterans. Progressive dyspnea (23 patients) and persistent cough (21 patients) were the predominant symptoms on presentation; these features developed approximately 14 weeks after SA ingestion. Physical examination revealed decreased breathing sounds and tachypnea with wheezing in 3 patients and crackles in 17 patients. The use of the accessory muscles was observed in 19 patients. No abnormality was detected in the complete blood count, serum biochemistry, serum alpha-1 antitrypsin concentration, urine analysis, and electrocardiography.

Malaysians have consumed SA for a long time; however, there are no reports of related side effects. In contrast, in Taiwan, several side effects have been reported, which may be due to a difference in the amounts of consumed SA [21]. Taiwanese people consume about 150 g of SA as opposed to about 100 ~ 200 g consumed by Malaysians.

One study reported that papaverine, which is a component of SA, results in the development of bronchiolitis obliterans [22]; however, this is questionable. Wang

Table 13.5 Clinical features of *Sauropus androgynous*-induced bronchiolitis obliterans

Total number	23 (male 0/female 23)	
Mean age (range)	39 (21–52)	
	Number (proportion)	
Symptoms		
Progressive dyspnea	23 (100%)	
Cough	21 (91%)	
Sputum	8 (34%)	
Oral ulcer	9 (39%)	
Palpitation	17 (73%)	
Insomnia	12 (52%)	
Physical examination		
Decreased breath sounds	3 (13%)	
Tachypnea	3 (13%)	
Wheezing	3 (13%)	
Crackles	17 (73%)	
Using of accessory muscles	19 (82%)	
	Mean (SD)	% predicted
Blood arterial gas		
pH	7.43 (±0.03)	
$PaCO_2$ (Torr)	39.0 (±6.7)	
PaO_2 (Torr)	72.0 (±12.0)	
SpO_2 (%)	94 (±3)	
Spirometry		
FEV_1 (L)	0.66 (±0.20)	26%
FVC (L)	1.52 (±0.36)	51%
TLC (L)	4.12 (±0.51)	95%
RV (L)	2.34 (±0.45)	177%
DL_{CO} (mL min^{-1} $mmHg^{-1}$)	12.1 (±4.1)	49%

SD standard deviation, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *TLC* total lung capacity, *RV* residual volume

reported that a more accurate histopathological classification of SA-associated lung disease is constrictive obliterative bronchitis/bronchiolitis with the participation of T-lymphocytes, macrophages, mast cells, eosinophils, and fibroblasts in its morphogenesis of the bronchioles or bronchi. The persistent accumulation of inflammatory cells was predominantly mediated by continued blood flow to the site of injury, eventually resulting in the irreversible fibrosis of the bronchioles and bronchi <3 mm in diameter. Obliterative arteriopathy was suspected of being only an indirect contributing factor [23].

In SA-induced bronchiolitis obliterans, respiratory failure sometimes progresses after SA ingestion has been discontinued. Moreover, corticosteroid therapy and immunosuppressive agents are usually administered; however, the condition is often resistant. Therefore, lung transplantation should be considered for treatment [24, 25]. This clinical course is not typically recognized as a DLI.

Table 13.6 Risk factors for pulmonary arterial hypertension

Definite	Possible	Likely	Unlikely
Aminorex	Cocaine	Amphetamines	Oral contraceptives
Fenfluramine	Phenylpropanolamine	L-tryptophan	Estrogen
Dexfenfluramine	St. John's Wort	Methamphetamines	Cigarette smoking
Toxic rapeseed oil	Chemotherapeutic agents	Dasatinib	
Benfluorex	Interferon α and β		
SSRI	Amphetamine-like drugs		

SSRI selective serotonin reuptake inhibitor

13.3.4 Pulmonary Arterial Hypertension

The Evian Conference in 1998 [9] reported that some drugs are the risk factors for the development of pulmonary arterial hypertension (PAH). In addition, these drugs were categorized into four types based on their incidence rate.

This categorization was followed by additional modification at the Venice meeting in 2003 [26], the Dana Point conference in 2008, and the Nice meeting in 2013 (Table 13.6) [27]. In this drug categorization scheme, "definite" indicates the demonstration of an association between a drug and PAH in large multicenter epidemiologic studies. "Likely" indicates the demonstration of such an association by a single-center case-control study or a multiple-case series. "Possible" indicates a demonstration of such an association based on case series, registries, or expert opinions. Finally, "unlikely" indicates that a drug has been studied in epidemiological studies and an association with PAH was not demonstrated [26–28].

Some of these drugs that pose a risk for the development of PAH are related to herbal medication (e.g., toxic rapeseed oil, cocaine, St. John's wort, and methamphetamine).

13.3.4.1 Toxic Rapeseed Oil

In 1981, in Madrid, Spain, the outbreak of toxic oil syndrome (TOS) was caused by the ingestion of a type of oil that was fraudulently sold as olive oil [29]. More than 15,000 children and adults were hospitalized in Madrid, complaining of fever, dyspnea, cough, skin rash, and a spectrum of gastric and neurologic symptoms. Approximately 300 died shortly after the onset of the disease, and a larger number developed a chronic disease [30].

PAH is one of the symptoms of TOS, showing an estimated frequency of 1 ~ 3% [30]. Garcia-Dorado D studied 38 patients with PAH due to toxic rapeseed oil [31], where the mean pulmonary arterial pressure of the patients was 40 ± 9 mmHg and the mean pulmonary to systemic vascular resistance ratio (Rp/Rs) was three times that of normal individuals (0.45 versus 0.15). However, cardiac index, pulmonary capillary wedge pressure, and left ventricular end-diastolic pressure remained within the normal range.

13.3.4.2 Cocaine

Long-term cocaine abuse causes left ventricular hypertrophy and systolic dysfunction [32]. In addition, many adverse cardiovascular events have been reported (e.g., dysrhythmias, endocarditis, and aortic dissection or rupture) [33, 34].

Moreover, pulmonary granulomatosis and pulmonary artery hypertension have been documented in chronic users of cocaine [35–37].

Significant reduction of the pulmonary vascular bed owing to the granulomatous process may result in pulmonary hypertension. The granulomatous process may be caused by insoluble agents that adulterate the addictive drug [36, 37].

Yakel DL Jr. (1995) measured the systolic pulmonary artery pressure (PAP) of 13 chronic intravenous cocaine users (aged 33.3 years; range, 23–41 years). Eight subjects had an elevated PAP (>30 mm Hg), three of whom had a PAP >40 mmHg [37].

13.3.4.3 St. John's Wort (*Hypericum perforatum*)

St. John's wort (*Hypericum perforatum*) is an herb of European origin that is perennial, bears yellow flowers, and is available worldwide.

St. John's wort is currently used for treating depression. A meta-analysis in 1996 [38] revealed that extracts of St. John's wort are more effective than placebo for the treatment of mild to moderately severe depression. Further, a double-blind randomized controlled trial [39] carried out in the United States was unable to demonstrate the efficacy of St. John's wort compared to placebo and sertraline—a selective serotonin reuptake inhibitor [SSRI]).

Hyperforin, one of the main components of the St. John's wort, increases synaptic serotonin and norepinephrine concentrations via an indirect and yet unknown mechanism [40]. Increasing synaptic serotonin and norepinephrine concentrations may be related to PAH, similar to SSRIs. In fact, an SSRI is categorized as a "definite" cause of PAH [28, 41].

13.3.4.4 Methamphetamine

Methamphetamine is synthesized from ephedrine extracted from *Ephedra sinica*. This plant has been used in China for more than 5000 years to stimulate circulation and for its antipyretic and antitussive properties. Ephedrine, which is the main ingredient of *Ephedra sinica*, was discovered by N. Nagai in 1885.

Ephedrine acts on parts of the sympathetic nervous system (SNS). The main mechanism of ephedrine is an indirect stimulation of the adrenergic receptor system through increasing the activity of norepinephrine at the postsynaptic α-adrenergic and β-adrenergic receptors. Although the action of ephedrine is less potent than that of adrenaline, its activation time is 7–10 times longer. Hence, ephedrine is used as a bronchodilator and vasopressor.

In contrast, methamphetamine is a strong agonist of trace amine-associated receptor 1 (TAAR1). Activated TAAR1 increases cyclic adenosine monophosphate (cAMP) production and completely inhibits the uptake of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT) in the plasma membrane [42, 43]. Moreover, methamphetamine induces efflux of neurotransmitters via the vesicular monoamine transporters (VMAT) [44]. Currently, methamphetamine is used to treat conditions such as narcolepsy and depression; however, it is strictly restricted worldwide because of its addictive nature and irritation to the central nervous system.

The proportion of stimulant use (amphetamines, methamphetamines, or cocaine) was investigated in 340 patients with idiopathic PAH, chronic thromboembolic PH (CTEPH) or PAH that was associated with other risk factors. A history of stimulant use was found in 28.9% of the patients diagnosed with idiopathic PAH, compared to 3.8% for the patients with PAH and a known risk factor, and 4.3% for patients with CTEPH [45].

Methamphetamines potently act on norepinephrine and dopamine transporters and rarely affect the serotonin transporter. Both serotonin and norepinephrine have vasoconstrictive and growth-modulating effects on smooth muscle cells, suggesting a possible involvement of methamphetamines in the development of PAH [46, 47].

Y. Sakurai reported a case of pulmonary hypertension due to bofutsushosan. Ephedra is a component of bofutsushosan [48]; thus, ephedra is probably involved in the development of PAH.

13.3.5 Pulmonary Arterial Thrombosis

Demonstrating a relationship between an administered drug and the development of pulmonary arterial thrombosis is difficult.

Yigit M reported a 41-year-old woman with a pulmonary embolism while on a high-dose course of panax tablets that contain extracts of *Tribulus terrestris*, *Avena sativa*, and *Panax ginseng* [49]. However, the pathophysiological mechanism of pulmonary embolism has not been demonstrated.

13.4 Therapy and Prognosis of a DLI due to Herbal Medication

There is no special treatment to protect against a DLI due to herbal medication. The Japanese Respiratory Society has proposed a treatment for DLI [4]. Any drug that is suspected of causing a DLI should be immediately discontinued in all cases. If continued treatment is necessary, the suspected drug should be replaced by one that is less likely to induce a lung injury.

Table 13.7 Proposed classification and treatment strategy for drug-induced interstitial pneumonia and acute lung injury [4]

Degree of severity	PaO_2	Treatment[a]
Mild	≧80 Torr	Discontinuation of the suspected drug
Moderate	≧60 Torr, <80 Torr	Discontinuation of the suspected drug
		Adrenocorticosteroid therapy
Severe	<60 Torr (PaO_2/FiO_2 < 300)	Discontinuation of the suspected drug mPSL pulse therapy for 3 days and then continuous adrenocorticosteroid administration

[a]The treatment information is provided for reference only. When a patient rapidly resolves after discontinuation of the suspected drug or responds to adrenocorticosteroid therapy, the dose of the steroid should be reduced

Regarding drug-induced IP, treatment should be determined using PaO_2 (Table 13.7). The most common type of drug-induced IP due to herbal medication is the allergic type; thus, most patients will have a good response to steroid therapy. However, ten patients with SST-induced IP have died in Japan [17]. Therefore, it is important to note that delayed diagnosis and treatment of a drug-induced IP due to herbal medication could result in death.

Bronchiolitis obliterans due to *Sauropus androgynus* is irreversible and resistant to treatment, similar to idiopathic bronchiolitis obliterans. Lung transplantation is the only solution for patients in the advanced stage of this disease. Some patients with bronchiolitis obliterans due to *Sauropus androgynous* have successfully received a lung transplant [24, 25]. Therefore, early detection and treatment are important.

13.5 Conclusion

Herbal medication is rarely suspected to be involved in a DLI. A detailed inquiry of the patients is important because some DLIs resulting from the use of herbal medication are irreversible.

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