



# Liver injury related to Japanese herbal medicines: clinical features and diagnosis

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## Abstract

The word “Kampo medicine” means the traditional Japanese herbal medicine. Even “natural herb” can cause drug-induced liver injury (DILI). In this review, the characteristics of Kampo medicine-induced liver injury (KMILI) are reported. The main causative herb involved in Kampo medicine is *Scutellariae Radix*. KMILI is based on certain hypersensitivity reactions. A small amount of Kampo medicine can cause liver injury, and KMILI can develop after a short latency period. The incidence of liver injury related to *Scutellariae Radix* is about 1%. KMILI is usually mild and not fatal. The latency period usually lasts 4 weeks to 24 weeks. Fatigue and loss of appetite are sometimes observed. Eosinophilia is not frequently observed. All three types of liver injuries are observed in KMILI: cholestatic, hepatocellular, and mixed types. In Japan, lymphocyte transformation test (LTT) has been generally used for the diagnosis of DILI; however, LTT is likely to yield false-positive result for Kampo medicines, and thus often leads to misdiagnosis in many cases. Recently, researchers reported that a specific human leukocyte antigen (HLA) genotype is possibly associated with KMILI. This hypothesis needs to be examined further. Although Kampo medicine is based on rich knowledge and experience that occurred over a period of thousands of years, much is still unknown about KMILI.

## Keywords

Drug-induced liver injury, Kampo medicine, incidence, lymphocyte transformation test, human leukocyte antigen

## Introduction

Among herbal medicines in the world, “Kampo medicine” means Japanese traditional herbal medicine. During the 1990s in Japan, unexpected adverse events related to some Kampo medicines were reported in the media [1]. Heated debates ensued over several adverse events of Kampo medicine. Although some people think that herbal medicines are harmless, many herbal components, such as ephedrine, pseudoephedrine, glycyrrhizin, sennoside, and berberine, have obvious pharmacological actions and adverse effects.

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Adverse effects of herbal medicines and herbal supplements are attracting attention among academic societies. At first, this report defines the differences between folk medicine and Kampo medicine, and then describes the incidence, clinical features, diagnosis, and treatment of Kampo medicine-induced liver injury (KMILI).

## What is Kampo medicine?

While folk medicine is usually made from a single herb. Kampo medicine is made by combining several herbs (Table 1), i.e., grass root, tree bark, plant stem, etc. The combination and the amount of each herb are specifically described in the classics such as *Shokanron* (written around AD 200). Kampo medicines have been used for several thousand years in the Eastern countries. It is not well known that today's Kampo extract preparations are listed in the formal pharmacopoeia in Japan. The amounts of specific components (glycyrrhizin etc.) in each herb are strictly regulated by numerical values.

**Table 1.** Typical Kampo medicines containing *Scutellariae Radix*

Kampo medicine	Components
Shosaikoto	7 herbs
Saikokeishito	9 herbs
Bofutsushosan	17 herbs & 1 mineral
Daisaikoto	8 herbs
Orengedokuto	4 herbs
Unseiin	8 herbs

The term “Kampo” originally means the traditional medicine transmitted from China; however, basic theory, prescription selection method, and component herbs are sometimes different between Kampo medicine and the current Chinese herbal medicine [2]. Kampo medicine has undergone unique development during the Edo period (AD 1603–1868) and other periods in Japan.

At present, many clinical trials for Kampo medicines have been scientifically conducted under strict control with standard products of Kampo medicines.

## Main causal herb responsible for KMILI

Most Kampo medicines are safe and cause little liver injury. Some Kampo medicines, including Shosaikoto, Saikokeishito, and Bofutsushosan, occasionally cause KMILI [3]. These medicines generally contain *Scutellariae Radix* (Table 1). The incidence of liver injury related to *Scutellariae Radix* is relatively higher than that related to other herbs. Kampo medicines those do not contain *Scutellariae Radix* merely induce drug-induced liver injury (DILI).

*Scutellariae Radix* is also used in Chinese herbal medicines. Several literatures have reported liver injury induced by “skullcap” which is the common name for *Scutellaria*. Clinical reports in Western countries have also suggested that hepatotoxic reactions can be induced by herbal preparations including skullcap of *Scutellaria* species [4, 5].

## Development of KMILI

In general, there are two development manners in DILI: 1) direct toxicity due to an excessive dose of the drug, 2) damage due to drug hypersensitivity. KMILI is fundamentally due to some hypersensitivity [6]; therefore, a small amount of Kampo medicine can induce liver injury and KMILI can develop after a short latency period [6] (the time between the start of the drug intake and the onset of DILI).

KMILI can repeatedly occur in a particular individual; however, most patients administered with Kampo medicines do not experience KMILI.

Recent researches have shown human leukocyte antigen (HLA) genotype variations are associated with allergic hepatotoxicity [7]. We have reported that HLA-DPA1\*02:02:02 is possibly associated with KMILI [8]. HLA typing may contribute both diagnosis and prediction of KMILI.

## Incidence of KMILI

In a university hospital department of Kampo medicine, we examined medical records of all patients from 1979 to 1999 [9]. Among 14,616 outpatients prescribed Kampo medicines, 0.04% patients had liver injury caused by Kampo medicine.

Thereafter we further examined the incidence of liver injury related to *Scutellariae Radix* in our clinic [10]. The study suggested that the incidence of liver injury related to *Scutellariae Radix* is 1.2%. Another report also suggested that the incidence related to *Scutellariae Radix* is 1.0% [3].

## Clinical features of KMILI

No definite risk factors of KMILI have determined. KMILI do not have a discernable relationship to a particular disease or a medical history. The latency period (the time between the start of the drug intake and the onset of DILI) usually lasts 4 weeks to 24 weeks (Table 2). In case of re-exposure, the latency period possibly becomes shorter (3 days, etc.).

**Table 2.** Typical findings of KMILI [3]

Items	Typical Findings
Male-female ratio	No bias
Causal herb	<i>Scutellariae Radix</i>
LTT	Often positive
Usual latency period	4–24 weeks
Usual recovery period	4–10 weeks
Eosinophilia	Not often
Total bilirubin	0.7–10.0 mg/dL

LTT: lymphocyte transformation test

Fatigue and loss of appetite are sometimes observed. Concomitant fever, eruption, jaundice, or itching is relatively few in the cases of KMILI. Eosinophilia is not frequently observed. The peak of eosinophilia may occur 1–2 weeks after the peak of alanine aminotransferase (ALT) or alkaline phosphatase (AP). All three types of liver injuries are observed in KMILI: cholestatic, hepatocellular and mixed types [9].

## Diagnosis

KMILI diagnosis mostly relies on the exclusion of alternative causes for liver injury; however, many diseases, including autoimmune hepatitis, primary biliary cholangitis, alcoholic hepatitis, pancreatitis, and DILI due to other drugs, are sometimes misunderstood as KMILI [9].

To diagnose DILI, Japanese physicians are currently reluctant to perform challenge test due to the opinion that challenge test should be avoided for patients who are thought to be suffering an adverse effect of a drug. Instead, the LTT has been prevalently utilized for the diagnosis of DILI in Japan [11].

LTT is based on the activation and expansion of the drug-specific lymphocytes following co-incubation of the patient's peripheral lymphocytes with the suspected drug *in vitro* [12]. In Western countries, LTT for specific drug hypersensitivity is considered either unreliable or experimental [13]. Previously we also reported that LTT for Kampo medicines is fundamentally unreliable because of the likelihood of false positive results [14]. Kampo medicines contain several immunomodulatory compounds, and some herbs have a mitogenic activity that can affect LTT.

Unfortunately, the challenge test using a suspected medicine is now the most reliable method of assessing the relationship between Kampo medicine and occurrence of liver injury. We have reported clinical features and safety of the hypersensitivity reaction induced by challenge tests using Kampo medicines [6]. In all 7 cases, the liver injuries induced by the challenge cleared within 2 weeks, and neither severe nor fatal liver injury was observed [6].

Therefore, the challenge test for suspected medicine could be allowed in the cases in which alternative treatments cannot be employed. Safety and availability of challenge test with Kampo medicines should be further examined.

Several diagnostic scales, such as the Roussel Uclaf Causality Assessment Method (RUCAM) scale, have been developed. However, many limitations and weaknesses of these scales have been pointed out [15]. Although RUCAM scale is also used for diagnosis of KMILI, RUCAM scale can yield false-positive result in some suspected cases. Japanese original scale, Digestive Disease Week-Japan (DDW-J) diagnostic scale that includes LTT as a diagnostic item, often yields false-positive result and has low specificity [16].

In our previous study, the assessment of KMILI was made based on 5 factors without any scales or scoring systems: period to onset of liver injury, course after cessation of drug, concomitant drugs, search for non-drug cause, and response to re-exposure [9]. Diagnosis of KMILI remains challenging and sincerely awaits the development of reliable biomarkers.

## **Treatment**

In most cases, KMILI recovers after withdrawal period of 4–10 weeks [8]. Fulminant hepatitis or fatal damage is seldom observed. Self-medication possibly causes late detection of liver damage and severe DILI. A few fatal cases caused by non-prescribed Kampo medicines have been reported in Japan [17]. Regular monitoring by physicians after administration of Kampo medicines is warranted.

## **Conclusions**

Diagnosis of KMILI is not easy to be made. Reliable biomarkers for KMILI have not been established. Based on the traditional use of Kampo medicine for thousands of years, the empirical wisdom of human has been concentrated in Kampo medicine. If Kampo medicines were inherently dangerous, they would have already disappeared by cultural selection.

## **Abbreviations**

DILI: drug-induced liver injury

HLA: human leukocyte antigen

KMILI: Kampo medicine-induced liver injury

LTT: lymphocyte transformation test

RUCAM: Roussel Uclaf Causality Assessment Method

## **Declarations**

### **Author contributions**

NM: Writing—original draft and Writing—review & editing.

### **Conflicts of interest**

The author declares that he has no conflicts of interest.

### **Ethical approval**

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

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### Copyright

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