Review

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Kampo medicine inducing drug-induced liver injury: A case report and systematic review

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SUMMARY Kampo medicine, comprising various conventional crude drug products, poses challenges in identifying adverse event causality. We present a case of severe liver injury following the administration of Saibokuto and attempted to identify the likely causative crude drug inducing liver injury through a systematic literature review. A 29-year-old woman developed severe liver injury approximately two months after Saibokuto administration, necessitating steroid pulse therapy for recovery. The literature search was conducted on February 15, 2023 in Japan. Using PubMed and the "Igaku Chuo Zasshi (ICHUSHI) database," two individuals independently selected studies published between January 1997 and February 15, 2023. The search focused on studies involving human subjects, published in either English or Japanese, and specifically investigated Kampo medicines categorized as over-the-counter or prescription drugs suspected as causative agents of drug-induced liver injury (DILI). Studies on health supplements, discontinued Kampo medicines, and autoimmune hepatitis, were excluded. As it is ethically impossible to rechallenge drugs that cause liver injury, this review primarily relied on case report literature. Through the review, 37 cases (men/women: 12/25, including present case) were analyzed, including 32 reports (36 cases) from 3,055 studies that met the inclusion criteria. Notably, 65.9% of cases were associated with Scutellariae radix, with onset occurring within 45 (1-730) days and recovery within 35 (7-184) days. Our case study and literature review underscore a prevalent association between liver injury and Kampo medicines containing Scutellariae radix. Vigilant liver function monitoring, particularly within the first 2 months of administration, is recommended, especially for formulations containing Scutellariae radix.

Keywords Kampo medicine, drug-induced liver injury, scutellariae radix, Saibokuto

1. Introduction

Recently, there has been a growing demand for complementary and alternative medicine (CAM) in the field of life sciences (*1*). CAM is extensively investigated as an approach to address various concerns related to cancer, such as pain, sleep disorders, fatigue, and relaxation, with practices such as yoga and meditation being widely utilized (*2,3*). Additionally, CAM therapies such as acupuncture and Ayurveda therapy have garnered significant attention for managing migraine headaches (*4*).

Among these alternative therapies, Kampo medicine holds a long history of use, particularly in Asian countries. In recent years, pharmaceutical companies have been marketing Kampo medicines as medicinal products, contributing to their growing utilization in the U.S. and other countries (*5,6*). In Japan, the use of Kampo medicines has evolved beyond the traditional "constitution-based" approaches to include evidence-based practices, integrating them into medical settings akin to Western medicine. Recent evidence indicated the widespread employment of Kampo medicine, including the use of "Yokukansan" for managing behavioral and psychological symptoms of dementia (BPSD) (*7*), "Daikenchuto" for post-abdominal surgery ileus (*8*), and "Kakkonto" for Coronavirus disease 2019 (COVID-19) (*9*). In 2021, out of 9.18 trillion yen in pharmaceutical production in Japan, approximately 208 billion yen was attributed to Kampo medicines and other related products. Since 2017, the overall production of Kampo medicines and related products, including those for general use, has increased by 21.7%, reflecting the recognition of their utility (*10,11*).

As the scope of indications for Kampo medicine continues to expand, patients from diverse backgrounds are receiving treatment. Consequently, adverse events not previously associated with Kampo medicine, such as interstitial lung disease (*12*), mesenteric phlebosclerosis (*13*), congestive heart failure (*14*), and drug-induced liver injury (DILI) (*15–17*), have been reported. This underscores the importance of updating safety information for Kampo medicines from a pharmacovigilance perspective.

In our recent experience, we encountered a patient who developed severe liver injury following the administration of Kampo medicine. In this manuscript, we present a case and provide a systematic review of information related to Kampo medicine-induced liver injury, aiming to comprehensively report our findings.

2. Materials and Methods

2.1. Ethics approval

The study was exempt from approval by the Institutional Review Board of Showa University, but written informed consent was obtained from patients for publication of this report in accordance with the journal's patient consent policy.

2.2. Literature survey

The literature search was conducted on February 15, 2023, at 6:00 PM in Japan. Two individuals independently selected relevant studies. The search focused on studies involving human subjects (adults or older), published in either English or Japanese, and specifically investigated Kampo medicines categorized as over-the-counter or prescription drugs suspected as the causative agents of DILI. The selected studies provided the patient information, admission examination findings, and treatment details related to drug-induced liver injuries. Kampo medicines are formulations that contain two or more crude drugs. Studies related to homeopathy, health supplements, herbal mixtures containing non-natural-derived components as primary ingredients, illegal drugs, recreational drugs, discontinued Kampo medicines, topical Kampo medicines, concomitant viral hepatitis, and autoimmune hepatitis were excluded. In addition, to limit liver injury caused by Kampo medicines, drugs that cause liver injury – anti-allergic agents, gout suppressants, hypoglycemic agents, anti-bacterial agents, anticonvulsants, antineoplastic agents, non-steroidal anti-inflammatory drugs, hydroxymethylglutaryl-CoA reductase inhibitors and acetaminophen, and liver injury associated with COVID-19 – were excluded.

Using PubMed and the "Igaku Chuo Zasshi (ICHUSHI) database," we conducted a literature search for studies published between January 1997 and February 15, 2023. The search terms for formula in PubMed were as follows: (((traditional chinese herb medicine) OR (traditional Chinese medicine) OR (Kampo) OR ("Medicine, East Asian Traditional"[Mesh])) AND ((Drug-induced liver injury)) OR ("Chemical and Drug Induced Liver Injury"[Mesh])) AND ((humans[Filter]) AND (1997/1/1:2022/12/31[pdat]) AND (English[Filter] OR Japanese[Filter]) AND (all adult[Filter]))NOT ("Anti-Allergic Agents"[Mesh]) NOT ("Gout Suppressants"[Pharmacological Action])NOT ("Hypoglycemic Agents"[Mesh]) NOT ("Anti-Bacterial Agents"[Mesh]) NOT ("Anticonvulsants"[Mesh]) NOT ("Antineoplastic Agents"[Mesh]) NOT ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) NOT ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) NOT ("Acetaminophen"[Mesh]) NOT ("Antirheumatic Agents"[Mesh]) NOT ("COVID-19"[Mesh]). The search terms for formula in ICYUSHI database were as follows; Medical Database "ICYUSHI": ((((Liver diseases/TH or Hepatic disorder/AL)) and ((Kampo medicine/TH or Kampo medicine/AL))) and (DT=1997:2022 and LA=Japanese, English and PT=Original article, Excluding conference proceedings and (CK=Humans) and (CK=Adult (19-44), Middle-aged (45-64), Elderly (65 and over)))).

2.3. Analysis of cases collected through literature survey

We conducted a systematic review and analyzed the timeline of liver injury manifestations in the cases that we encountered, classifying them into three types: hepatocellular injury, cholestatic, and mixed type (*18*). The time to onset and the time to recovery of liver injury were divided into intervals of 1, 2, 3, 4, and 5 months.

Furthermore, we compiled a list of the Kampo medicines taken by the patients under investigation and categorized them according to their constituent components. We visually analyzed the relationship between the severity of liver injury using total bilirubin (T-bil), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) values, and the components of Kampo medicine. To identify the potential components responsible for DILI, we calculated the proportion of cases with T-bil and ALT at grade 4, and ALP at grade 2 or higher, as assessed by Common Terminology Criteria for Adverse Events version 5.0 (CTCAE ver. 5.0).

3. Results

3.1. Case presentation

In September 2021, a 29-year-old woman was diagnosed with gastroesophageal reflux disease (GERD) and initiated treatment with vonoprazan. In July 2022, she sought care at a local clinic due to persistent pharyngeal discomfort and fullness, prompting the addition of Saibokuto to her medication regimen alongside

vonoprazan. By September 2022, she experienced sudden fatigue and difficulty walking, leading to a visit to the emergency department, where the cause remained unidentified. Subsequently, Rikkunshito was incorporated into her treatment regimen. The next day, feeling generally unwell, she revisited her local clinic, and further sulpiride was added to her medication regimen.

In October 2022, while still adhering to vonoprazan, Saibokuto, Rikkunshito, and sulpiride, the patient developed jaundice and brownish urine. Concerned about potential liver injury, she consulted her primary care physician, who immediately admitted her to the hospital on October 5th. Upon admission (day 1), her blood test results showed elevated levels of ALP at 103 U/L, aspartate aminotransferase (AST) at 1,476 U/L, ALT at 1,263 U/L, T-bil at 11.6 mg/dL, direct bilirubin (D-bil) at 6.8 mg/dL, and a prolonged prothrombin time (PT) at 73%. These results indicated grade 4 severity for ALT, AST, T-bil, and D-bil, according to CTCAE ver. 5.0. DILI was suspected to be the cause of severe hepatic dysfunction, prompting discontinuation of vonoprazan, Saibokuto, Rikkunshito, and sulpiride. Despite extensive examinations, including abdominal ultrasonography and computed tomography, the specific cause of liver injury remained unidentified.

On day 7, her blood test results showed improvements in ALP (84 U/L), AST (1,075 U/L), ALT (1,021 U/L), T-bil (17 mg/dL), and D-bil (12.6 mg/dL), with PT at 68%. On day 8, the patient was transferred to Showa University Hospital. Upon admission, she presented with generalized jaundice, yellowing of the skin, and yellowing of the eyes. Her blood test results at Showa University Hospital showed ALP at 91 U/L, AST at 969 U/L, ALT at 1,007 U/L, T-bil at 19.1 mg/dL, D-bil at 14.4 mg/dL, and PT at 60%. Based on the Roussel-Uclaf Causality Assessment Method (RUCAM) (*19*) scoring of diagnostic criteria for DILI (*18*), she received a score of 9 points, raising suspicion of DILI of the hepatocellular injury type. In addition, a drug-induced lymphocyte stimulation test (DLST) and liver biopsy were performed using the suspected drugs vonoprazan, Saibokuto, Rikkunshito, and sulpiride. On day 9, she received a steroid pulse (methylprednisolone injection 1,000 mg/body) for 3 days, and on day 13, her laboratory findings showed improvements with AST at 56 U/L, ALT at 218 U/L, T-bil at 3.9 mg/dL, and D-bil at 1.6 mg/dL. On day 15, the DLST results indicated a stimulation index of 9.4 for Saibokuto, leading to a diagnosis of DILI due to Saibokuto. On day 18, her condition improved further with AST at 55 U/L, ALT at 125 U/L, T-bil at 3.3 mg/dL, and D-bil at 0.7 mg/dL, and she was discharged. At her first outpatient visit on day 23 after discharge, her blood test results showed AST at 40 U/L, ALT at 67 U/L, T-bil at 2.6 mg/dL, D-bil at 0.5 mg/dL, and overall improvement of jaundice (Figure 1).

3.2. Systematic review results and background of study patients

A total of 3,055 articles were extracted, including 2,663 articles from PubMed, and 390 articles from the "ICYUSHI database", and 2 articles from a manual search. Among them, 12 articles were excluded due to duplication between PubMed and "ICYUSHI database", 2,809 articles were excluded based on their titles, and an additional 173 articles were excluded based on their abstracts (Figure 2). The remaining articles were evaluated by two reviewers for publication year, patient characteristics (age, sex, and medical history), number of days until liver injury manifestation, severity of liver injury, suspected Kampo medicines, sources of Kampo medicines, and number of days until recovery. Following this assessment, 32 case reports/case series studies and our presented cases involving 37 patients including present case were selected for the final analysis (Table 1).

The limitation of this systematic review is that re-administration of the drug causing liver injury may lead to anaphylaxis, and prospective clinical trials are difficult to conduct; thus, the results of the literature review focused on case reports.

3.3. Types of liver injury and days to liver injury manifestation in study patients

The median age of the patients (12 men and 25 women) was 53 years (range: 29–78 years). Their medical history included hypertension, diabetes, and cholecystolithiasis. The median number of days until liver injury manifestation for all patients was 45 (range: 1–730), and the median time to recovery was 35 days (range: 7–184) (Table 1). Among the patients, 18 had hepatocellular injury-type liver injury, 8 had cholestatic injury, and 11 had mixed injury. Patients who developed liver injury within one month after initiation of suspected Kampo medicines had the highest frequency, accounting for 37.8% of the total cases. For the hepatocellular injury type, the majority of patients developed liver injury within 1 month, whereas for the cholestatic type, 100% developed liver injury within 3 months. There were no significant differences in the time period from Kampo medicine intake to liver injury manifestation in the mixed type (Figure 3). Most patients recovered within 2 months of treatment after discontinuing Kampo medicine, accounting for 83.8% of all patients. The percentages of patients who recovered after more than 2 months were 2.7, 5.4, and 8.1% for the hepatocellular injury, cholestatic, and mixed types, respectively (Figure 3).

3.4. Liver injury severity and characteristics of constituent components in Kampo medicines

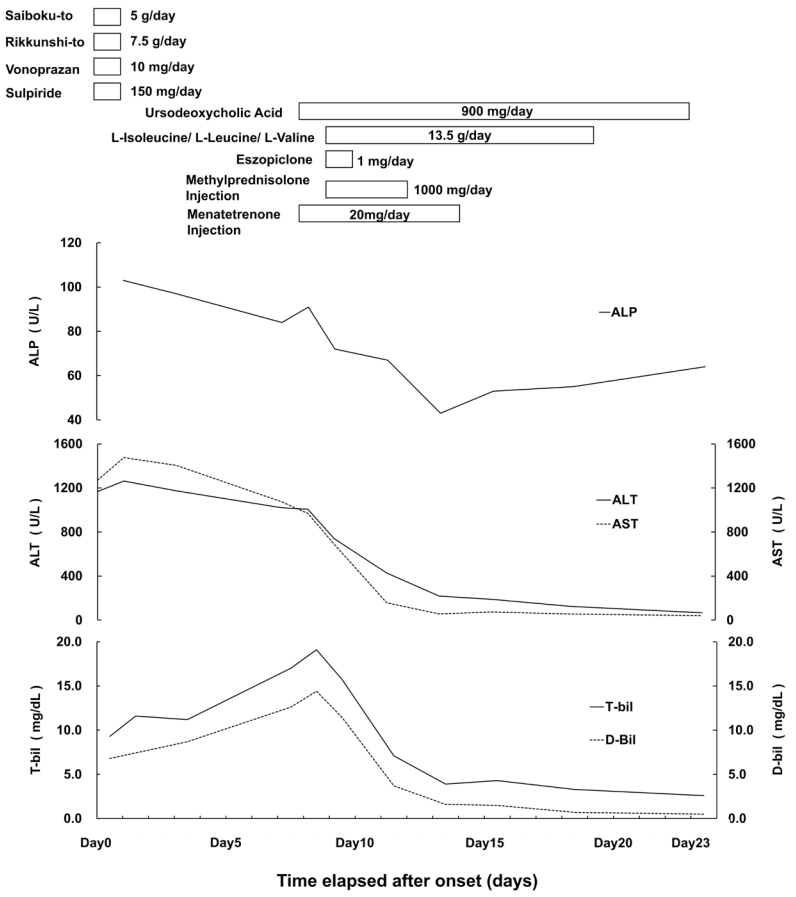

Figure 1. Clinical course of the present case. Description of the liver function laboratory values and medication history of a 29-year-old woman after hospital admission.

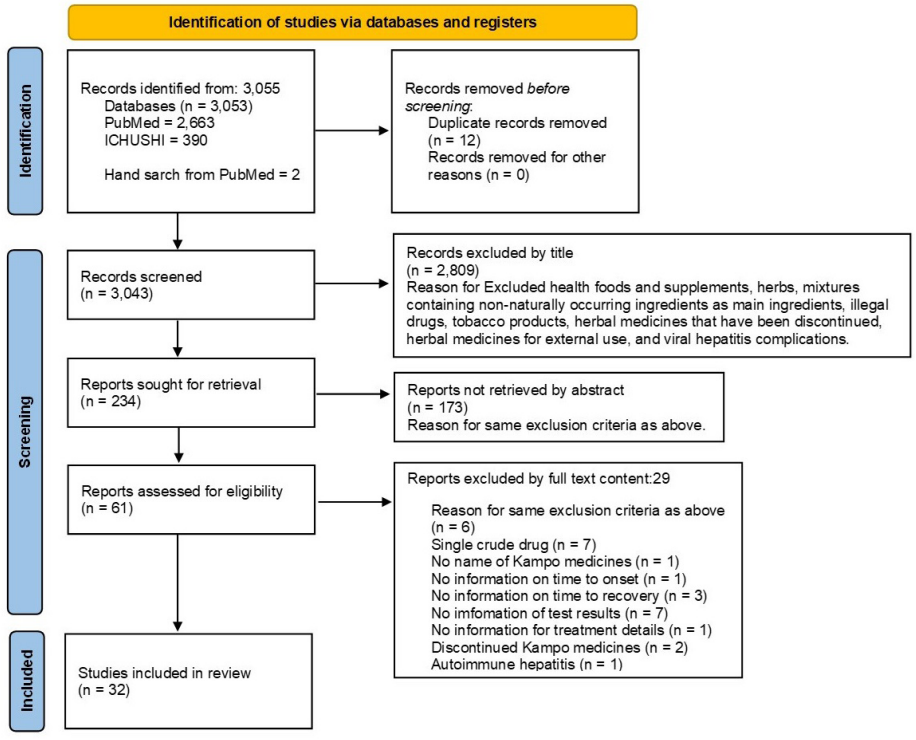

Figure 2. Systematic review of PRISMA flow diagram. Flowchart showing the literature survey on Kampo medicine-induced liver injury from PubMed and ICYUSHI databases.

Table 1. Kampo medicines inducing liver injury from literature survey

Author	Year	Age (years)	Gender	Medical history	Suspect drug source	Suspect drug	Type of DILI	Time to onset of DILI (days)	The Grade of T-bil / ALT/ALP/	Time to recovery from DILI (days)	Treatment
Yoshikubo, *et al.* (*20*)	1997	31	Female	12 weeks of pregnancy	Prescription drug	Bukuryoingohangekobokuto	Hepatocellular injury type	42	4/4/0	37	Suspect drug stopped, Plasma exchange, hemodialysis and mPSL 1000 mg/day 2 days
Matsuda, *et al.* (*21*)	1997	65	Male	Diabetes	Prescription drug	Daisaikoto	mixed type	50	1/4/2	50	Suspect drug stopped
Shiota, *et al.* (*22*)	1997	78	Female	Rheumatoid arthritis	Over-the-counter drugs	Hangeshoshinto	Cholestatic type	10	0/2/1	57	Suspect drug stopped
Takeshima, *et al.* (*23*)	1997	49	Female	Duodenal ulcer	Prescription drug	Shosaikoto	Mixed type	100	0/4/2	30	Suspect drug stopped
Nakai, *et al.* (*24*)	1998	71	Male	None	Over-the-counter drugs	Shakuyakukanzoto	cholestatic type	21	4/3/3	45	Suspect drug stopped, UDCA, and GA
Okada, *et al.* (*25*)	1999	60	Male	Hypertension	Prescription drug	Hangeshoshinto	Cholestatic type	60	0/2/2	60	Suspect drug stopped and GA
Nagai, *et al.* (*26*)	1999	49	Female	Internal hemorrhoid	Prescription drug	Otsujito	Hepatocellular injury type	101	0/4/2	28	Suspect drug stopped and GA
Kamioka, *et al.* (*27*)	1999	46	Female	None	Over-the-counter drugs	Unseiin	Hepatocellular injury type	300	0/4/1	25	Suspect drug stopped and GA
Kurai, *et al.* (*28*)	2000	48	Female	None	Prescription drug	Otsujito	Hepatocellular injury type	69	1/4/2	93	Suspect drug stopped, UDCA, and GA
Ozawa, *et al.* (*29*)	2001	46	Female	Hypertension	Prescription drug	Bofutsusyosan	Mixed type	425	4/3/1	80	Suspect drug stopped, Plasma exchange, Hemodialysis, UDCA, GA, and mPSL 1000 mg/day 3 days
Ishii, *et al.* (*30*)	2001	64	Male	Myocardial infarction	Over-the-counter drugs	Pian tze huang	Mixed type	305	0/3/1	28	Suspect drug stopped, UDCA, and GA
Kamigaki, *et al.* (*31*)	2001	66	Male	Hypertension	Prescription drug	Kakkonto	Mixed type	10	2/2/1	51	Suspect drug stopped, UDCA, and GA
Tani, *et al.* (*32*)	2001	57	Male	None	Prescription drug	Saibokuto	Cholestatic type	9	2/1/2	36	Suspect drug stopped, UDCA, GA, and PSL 30 mg/day tapered off.
Gabriella, *et al.* (*33*)	2002	48	Male	Psoriasis	Over-the-counter drugs	Fu Fang Qing Dai Wan	Hepatocellular injury type	30	2/4/2	56	Suspect drug stopped.
Yamamoto, *et al.* (*34*)	2003	35	Male	None	Prescription drug	Bofutsusyosan	Hepatocellular injury type	215	4/4/3	36	Suspect drug stopped and UDCA
Hosonuma, *et al.* (*35*)	2003	42	Female	None	Over-the-counter drugs	Saikokeishikankyoto	Hepatocellular injury type	30	1/4/2	31	Suspect drug stopped.
Hosonuma, *et al.* (*35*)	2003	42	Female	None	Prescription drug	Nyoshinsan	Hepatocellular injury type	1	0/4/2	14	Suspect drug stopped.
Li-Ming, *et al.* (*36*)	2006	52	Female	Cholecystolithiasis	Prescription drug	Shosaikoto	Hepatocellular injury type	45	1/4/1	54	Suspect drug stopped.

UDCA: Ursodeoxycholic acid, GA: glycyrrhizin acid, T-bil: total bilirubin, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

Table 1. Kampo medicines inducing liver injury from literature survey (continued)

Author	Year	Age (years)	Gender	Medical history	Suspect drug source	Suspect drug	Type of DILI	Time to onset of DILI (days)	The Grade of T-bil / ALT/ALP/	Time to recovery from DILI (days)	Treatment
Uchiyama, *et al.* (*37*)	2007	54	Male	Diabetes, Hypertension, Myocardial infarction	Prescription drug	Hangeshoshinto	Hepatocellular injury type	4	4/4/3	59	Suspect drug stopped, UDCA, and PSL 40 mg/day followed by mPSL 1000 mg/day 3 days
Motoyama, *et al.* (*38*)	2008	37	Female	None	Over-the-counter drugs	Bofutsusyosan	Hepatocellular injury type	60	4/4/3	20	Suspect drug stopped, GA, and PSL 40 mg/day
Irie, *et al.* (*39*)	2008	55	Female	None	Prescription drug	Nyoshinsan, Saffron	Mixed type	94	4/4/3	35	Suspect drug stopped and UDCA
Sannomiya, *et al.* (*40*)	2009	54	Female	Hypertension	Prescription drug	Bofutsusyosan	Hepatocellular injury type	21	2/4/1	15	Suspect drug stopped and GA
Sannomiya, *et al.* (*40*)	2009	52	Female	Basedow's disease	Prescription drug	Bofutsusyosan	Hepatocellular injury type	120	2/4/2	36	Suspect drug stopped, UDCA, and GA
Tanaka, *et al.* (*41*)	2011	32	Male	None	Over-the-counter drugs	Bofutsusyosan	Cholestatic type	60	4/4/3	20	Suspect drug stopped.
Futenma, *et al.* (*42*)	2012	68	Female	Knee osteoarthritis	Prescription drug	Boiogito	Mixed type	35	0/2/1	35	Suspect drug stopped.
Futenma, *et al.* (*42*)	2012	72	Female	Hypertension	Prescription drug	Boiogito	Cholestatic type	21	2/2/2	7	Suspect drug stopped
Negishi, *et al.* (*43*)	2014	57	Male	None	Prescription drug	Hochuekkito	Cholestatic type	7	4/3/2	184	Suspect drug stopped, UDCA, and GA
Maruyama, *et al.* (*44*)	2014	61	Female	Diabetes, Dyslipidemia, Hypertension	Prescription drug	Saireito	Mixed type	29	1/4/3	120	Suspect drug stopped
Dohmen, *et al.* (*45*)	2015	43	Female	Anxiety neurosis, Dyslipidemia, Sinusitis	Prescription drug	Shin'iseihaito	Mixed type	75	2/4/3	42	Suspect drug stopped
Oikawa, *et al.* (*46*)	2015	58	Female	None	Prescription drug	Saikokeishikankyoto	Mixed type	7	0/2/1	14	Suspect drug stopped
Ozeki, *et al.* (*47*)	2017	51	Female	None	Prescription drug	Bofutsusyosan	Hepatocellular injury type	60	2/4/2	9	Suspect drug stopped
Shimada, *et al.* (*48*)	2018	67	Female	Cholecystolithiasis	Prescription drug	Shosaikoto	Cholestatic type	4	1/2/1	15	Suspect drug stopped
Shimada, *et al.* (*48*)	2018	68	Female	Cholecystolithiasis	Prescription drug	Saikokeishikankyoto	Hepatocellular injury type	21	1/4/2	33	Suspect drug stopped
Shinohara, *et al.* (*49*)	2019	60s	Male	Atrial fibrillation, Cerebral infarction	Over-the-counter drugs	Ryutanshakanto	Hepatocellular injury type	730	1/4/2	12	Suspect drug stopped, UDCA, and GA
Yamamoto, *et al.* (*50*)	2020	36	Female	Irritable bowel syndrome	Prescription drug	Keishakuchimoto, Kamikihito	Mixed type	112	0/1/0	77	Suspect drug stopped
Funakoshi, *et al.* (*17*)	2021	59	Female	Lung cancer	Prescription drug	Hanshiren, Zenshikunshito, Ninjin'yoeito	Hepatocellular injury type	16	2/4/2	14	Suspect drug stopped
Our case	2022	29	Female	None	Prescription drug	Saibokuto	Hepatocellular injury type	76	4/4/1	18	Suspect drug stopped, UDCA, and mPSL 1000 mg/day 3 days

UDCA: Ursodeoxycholic acid, GA: glycyrrhizin acid, T-bil: total bilirubin, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

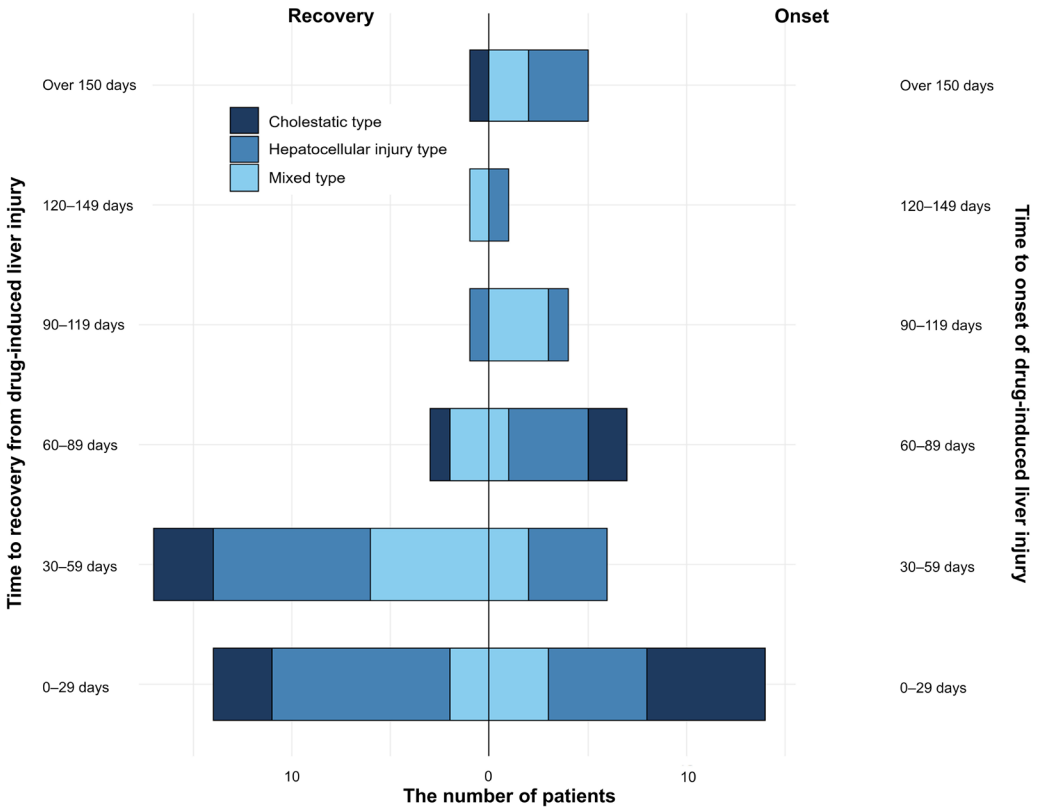

Figure 3. Time to onset and recovery by type of drug-induced liver injury. Time to onset and time to recovery from drug-induced liver injury are shown for cases from the literature survey.

Regarding the suspected Kampo medicines responsible for liver injury in the study patients, Bofutsushosan was reported in 7 cases, whereas Saikokeishikankyoto, Shosaikoto, and Hangeshashinto were each reported in 3 cases. Among these, 28 cases involved Kampo medicines categorized as prescription drugs, and nine cases involved Kampo medicines categorized as over-the-counter drugs. In this systematic review, 41 drugs were suspected in 37 cases investigated. A heatmap was created for each patient to illustrate the constituent components of the suspected Kampo medicines related to liver injury. According to the heatmap for T-bil grade 4 level, Glycyrrhizae radix (24.3%) was most frequently found in suspected Kampo medicines, followed by Scutellariae radix (18.9%) and Zingiberis rhizoma (18.9%) (Figure 4). Similarly, for ALP grade 2 level, the order was Glycyrrhizae radix (43.2%), Scutellariae radix (40.5%), and Zingiberis rhizoma (29.7%) (Figure 4), whereas for ALT grade 4, Scutellariae radix (56.8%) was the most frequently found in suspected Kampo medicines, followed by Glycyrrhizae radix (51.6%), Zingiberis rhizoma (35.1%), and Angelicae radix (35.1%) (Figure 4). Glycyrrhizae radix and Scutellariae radix are commonly found in suspected Kampo medicines associated with liver injury based on T-bil, ALT, and ALP levels.

4. Discussion

In this study, we present cases of severe liver injury associated with Kampo medicine, a traditional medicine widely used in Japan. Additionally, we conducted a systematic review to compile data on Kampo medicine-induced liver injury, focusing on the differences in the types of liver injury and the time of manifestation.

The patients that we encountered had a history of alcohol consumption approximately once every 1 to 2 months. Upon admission, tests for hepatitis A, B, C, and E, cytomegalovirus infection, and Epstein-Barr virus infection were all negative. Antinuclear antibodies were also negative, and liver biopsy did not reveal any abnormalities. DILI can be classified as hepatocellular, cholestatic, and mixed type (*18,51*). In this case, hepatocellular injury with jaundice was present, necessitating hospitalization due to the high risk of severe liver failure and poor outcomes (*52*). This type of hepatocellular injury was the most frequent type of liver injury observed in this systematic review. Furthermore, the time-to-onset of adverse events was consistent with the early onset type.

Treatment of DILI hepatoprotective drugs (*53*). In our cases, improvement was not observed upon discontinuation but was achieved through steroid pulse

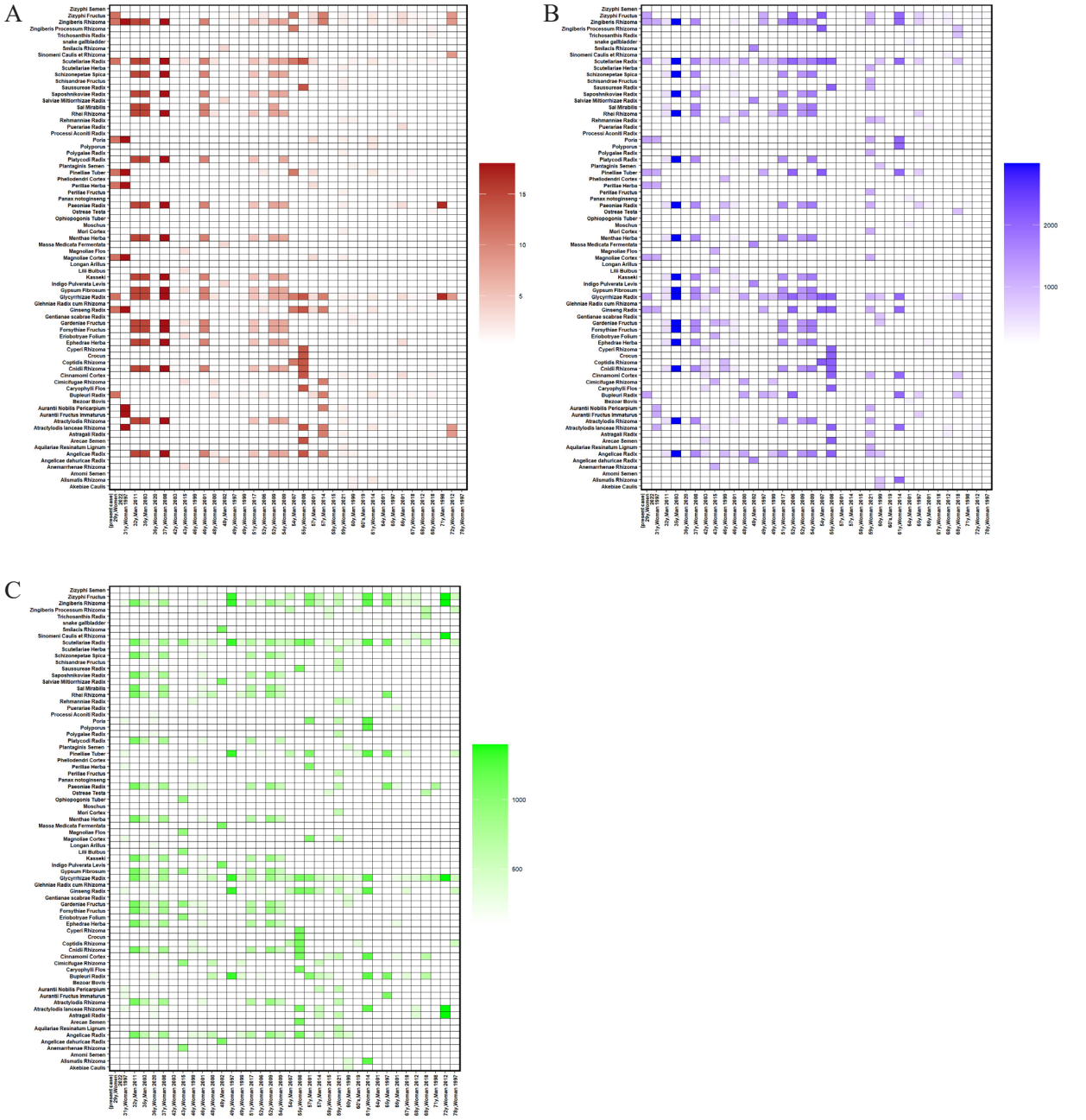

Figure 4. Severity of Kampo medicines inducing liver injury based on cases from literature survey. The correlation between the severity of Kampo medicines and the laboratory values for each patient in the literature survey is displayed in the color shade. (**A**) T-bil, (**B**) ALT, and (**C**) ALP. T-bil: total bilirubin, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

therapy. A systematic review found two cases (*34,49*) of hepatocellular injury requiring plasma exchange and hemodialysis, both with severe liver injury that improved after steroid pulse therapy. However, in both cases, the liver injury improved the day after the steroid pulse, which is similar to the present case. As acute liver failure occurs in severe cases of DILI, steroid pulse therapy may be used to prevent severe disease (*54,55*). Early steroid pulse therapy is believed to inhibit the progression of liver failure by suppressing hepatocyte destruction and microvascular damage via the immune response (*56*), and our patient also recovered quickly and was discharged from the hospital after steroid pulse therapy.

In this systematic review, we primarily relied on case report literature to evaluate the drugs that cause liver injury, the time to onset, the time to recovery, and the severity of the injury that needed to be assessed. According to the results of this systematic review, 41 components of suspected Kampo medicines contained 80.5% Glycyrrhizae radix and 65.9% Scutellariae radix. Glycyrrhizae radix has been frequently reported to cause pseudoaldosteronism, whereas Scutellariae radix is commonly associated with interstitial pneumonia and liver injury. Specifically, Scutellariae radix was found in 27 formulations (65.9%), including Bofutsushosan, Hangeshashinto, Nyoshinsan, Otsujito, Ryutanshakanto,

Saibokuto, Saireito, Shin'iseihaito, and so on. The possibility of Scutellariae radix as a cause of DILI has been considered in previous studies (*57,58*).

Glycyrrhizae radix is present in 73.6% of Japanese medicinal Kampo medicines (*11*). To the best of our knowledge, Glycyrrhizae radix associated DILI has never been reported before. Glycyrrhizin, a major component of Glycyrrhizae radix, and its metabolite glycyrrhetinic acid acts on hepatocyte cell membranes, reducing enzymes release from hepatocytes and exerting a protective effect on hepatocytes (*59*). Furthermore, it has been suggested that baicalin, the major component of Scutellariae radix, may act as a hapten, causing allergic reactions and resulting in cellular damage (*60*). Additionally, in the present case, the patient was administered with Saibokuto, which contains both Glycyrrhizae radix and Scutellariae radix, and Rikkunshito, which contains Glycyrrhizae; however, but the DLST results in this case were positive for Saibokuto. When Rikkunshito was added, the patient was already suffering from fatigue and anorexia, which are early symptoms of liver injury. It has been suggested that careful consideration is required, especially for Kampo medicines containing Scutellariae radix.

Many Kampo medicines contain Scutellariae radix, which is also found in over-the-counter drugs (*57*). Owing to the recent increase in CAM use, the number of suspected cases of DILI caused by Kampo medicine is expected to increase. Since cases involving Scutellariae radix may be severe, as in this case, it is important to confirm the formulation of Kampo medicine, take appropriate action, and instruct the patient to avoid future use of both medical and over-the-counter medications.

Kampo medicines contain multiple active ingredients with diverse therapeutic effects. However, identifying the specific cause becomes challenging (*53*). Moreover, rechallenging patients carries a high risk, the cause of which remains unclear. Therefore, conducting a prospective study is ethically challenging. In addition, the literature review focuses on case reports of liver injury caused by Kampo medicines. It is important to note that the study may be biased due to the small proportion of Kampo medicines used in comparison to Western medicines and the fact that case reports of Kampo medicines are not very common.

5. Conclusions

In this study, we compiled information on Kampo medicine-induced liver injury and highlighted the possibility of different time to onset for each type of liver injury, and the likelihood of Scutellariae radix as a suspected component. In the medical field, particularly when administering Kampo medicines containing Scutellariae radix, monitoring liver function for at least two months from the start of administration may be crucial owing to the potential risk of hepatotoxicity.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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