Safety of prescribed herbal medicines for hepatic and renal function of polypharmacy patients with stroke
A single-center retrospective study

JunSeok Kim, KMD, BS[a], WooSeok Jang, KMD, PhD[a],* iD

Abstract

In Korea, herbal medicines (HMs) are primarily used to treat diseases. Patients with stroke are generally older and take several conventional medicines (CMs) to address other underlying diseases, which is known as polypharmacy. Therefore, there is a growing concern about hepatotoxicity and nephrotoxicity due to drug interactions between HMs and CMs. Therefore, this study retrospectively investigated liver and renal tests in patients with stroke treated with polypharmacy to clarify the safety of simultaneous HM and CM administration. The medical records of 111 patients with stroke treated at a single center and who met the inclusion criteria between March 1, 2017, and March 1, 2022, were reviewed. The HMs and HM prescription frequency, CMs, and liver and kidney test results were recorded. Additionally, the Roussel Uclaf Causality Assessment Method and Kidney Disease Improving Global Outcome scores were documented, which are standard criteria for assessing liver and kidney injury, respectively. The study included 53 men and 58 women (average age: 67.8 years). On average, the patients took 6 types of CMs. No patient showed liver injury during the co-administration of CMs and HMs. Only 1 patient had initial hepatic damage but recovered after taking HMs. Furthermore, 2 patients had liver test abnormalities 2 times the upper limit of normal, possibly from Seogyeong-tang and atorvastatin, with Roussel Uclaf Causality Assessment Method scale scores of 3 and 5, respectively. No patient had a renal injury. HM is safe for patients with stroke taking multiple CMs. However, consulting an HM expert is essential to avoid hepatotoxicity, nephrotoxicity, and other adverse effects. These results highlight the benefits of Korea's dual medical system.

Abbreviations: AKI = acute kidney injury, ALP = alkaline phosphatase, ALT = alanine transaminase, CM = conventional medicine, Cr = creatinine, DILI = drug-induced liver injury, DM = diabetes mellitus, HILI = herb-induced liver injury, HL = hyperlipidemia, HM = herbal medicine, HTN = hypertension, KPIC = Korea Pharmaceutical Information Center, RUCAM = Roussel Uclaf causality assessment method, ULN = upper limit of normal.

Keywords: hepatotoxicity, herbal medicine, nephrotoxicity, polypharmacy, Roussel Uclaf causality assessment method, stroke patients.

1. Introduction

In Korea, herbal medicines (HMs) are commonly used to treat diseases, and HM use is gradually increasing worldwide.[1] Therefore, concerns about liver and renal safety are also growing. Many studies have addressed liver and kidney damage after HM use, but the results are contradictory due to varied research methods.[2] Additionally, studies on specific disease groups are inadequate.

Korean medical treatments, such as HMs, are becoming more popular for patients with stroke since there is no definite treatment or single rehabilitation intervention that definitively promotes recovery.[3] However, patients with stroke are generally older and take multiple conventional medicines (CMs) for underlying diseases, which is known as polypharmacy. Consequently, concerns about hepatotoxicity and nephrotoxicity due to CM and HM drug interactions are growing.

Post-stroke medications focus on recurrence prevention. Therefore, they primarily address the risk factors for stroke, including hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), and atrial fibrillation. Furthermore, patients experiencing ischemic stroke and arrhythmia are frequently prescribed antithrombotic agents, which are not for neurological recovery but for prevention.[3] Therefore, they are prescribed throughout the patient's lifetime.

Many studies have explored the efficacy of HM after stroke. However, safety studies regarding simultaneous CM and HM administration and the frequency of HM intake in patients

with stroke are lacking. Therefore, this study evaluated the HM prescription frequency and liver and kidney safety of polypharmacy in patients with stroke receiving HMs in a single center to elucidate any harmful interactions.

2. Materials and Methods

2.1. Ethical approval

This study was conducted after approval by the Institutional Review Board of Daegu Haany University Korean Medicine Hospital (DHUMC-D22008-ETC-01). The Institutional Review Board review stated this research qualifies for an exemption from the requirement for informed consent since there is no reason to estimate the refusal of consent from the patients and that the risk to the patients is extremely low even if the consent is waived.

2.2. Study design

2.2.1. Subjects and criteria. The medical records of patients with stroke hospitalized in the Department of Korean Internal Medicine, Cardiovascular and Neurologic Diseases Center, Daegu Korean Medicine Hospital of Daegu Haany University, Daegu, Korea, between March 1, 2017, and March 1, 2022, were retrospectively reviewed. Patients diagnosed with stroke based on the International Classification of Diseases, 10th revision codes I60–I63 and I69, who were hospitalized for ≥ 20 days were included. Furthermore, all patients had blood tests that included liver and renal markers before the HM prescription and at least 1 liver and renal marker follow-up. Patients without a blood test before the HM prescription and without a liver and renal test follow-up were excluded, as well as those not receiving HMs or distilled HMs. CM use of any kind throughout the study period was permitted (Fig. 1).

Korea has a dual medical system. Therefore, all CMs and HMs were prescribed by medical and Korean medicine doctors, respectively. Furthermore, all HMs were prescribed by Korean medicine doctors with > 10 years of clinical experience after completing a regular, 6-year university-level Korean medicine course and a 4-year hospital training course.

2.2.2.

Data collection. The following information was collected:

(1) Patient characteristics: age, sex, hospitalization duration, and stroke type (infarction or hemorrhage).

Figure 1. Inclusion and exclusion criteria.

(2) Liver test: aspartate transaminase, alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase levels (if liver abnormalities were present), medication history, and liver-related past medical history.
(3) Renal function: serum blood urea nitrogen and creatinine levels, relevant medical history (e.g., kidney disease), and medication history.
(4) HM prescription frequency: the prescription frequency was calculated by adding the types of HMs prescribed divided by the number of prescription days.
(5) Polypharmacy: the average number of prescribed CMs was determined. Additionally, the Korea Pharmaceutical Information Center (KPIC) classifications for CMs related to HTN, DM, HL, and antithrombotic medications were identified; HTN, DM, and HL are risk factors for stroke.

2.3. Assessment

2.3.1. Drug-or herb-induced liver injury (DILI or HILI). The liver test results were classified into abnormal test and liver injury groups. Liver test abnormalities were subdivided by period: at the time of hospitalization (initial), before HM prescription, and during hospitalization.

Liver injury was based on the Roussel Uclaf Causality Assessment Method (RUCAM) scale. Specifically, liver injury was present if the ALT level was > 5 times the upper limit of normal (ULN) and/or the ALP level was > 2 times the ULN. Here, the presence of liver damage, as well as an ALT level > 2 times ULN (even without liver damage), was assessed by the RUCAM scale. The R-value was defined as the ratio of the serum ALT to ALP level ([ALT/ALT ULN]/ [ALP/ALP ULN]). The liver injury types were classified as: hepatocellular: $R \geq 5$, cholestatic $R \leq 2$ or mixed: $2 < R < 5$. Subsequently, based on the RUCAM score, a causal relationship between the drug (CM or HM) and the liver injury event was assigned: highly probable (>9), probable (6–8), possible (3–5), unlikely (1–2), or excluded (≤0).[4] If the results were not within a normal range and did not fit the liver injury criteria, they were classified as liver test abnormalities.

2.3.2. Renal injury criteria. Acute kidney injury (AKI) was based on the Kidney Disease Improving Global Outcomes clinical practice guidelines. If the serum creatinine level increased by > 0.3 mg/dL (26.5 μmol/L) within 48 hours or ≥ 1.5 times the baseline within 7 days or if the urine output was < 0.5 mL/kg/ hour for 6 hours, then the patient was diagnosed with AKI.[5]

3. Results

3.1. Patient characteristics

In total, 111 patients with stroke met the inclusion criteria. The average age and hospitalization duration were 67.8 years and 72.6 days, respectively. Overall, 81 patients had cerebral infarction or related sequelae, and 30 had a cerebral hemorrhage or related sequelae (Table 1).

3.2. CM use

On average, each patient took 6 types of CMs. The patient's medications were divided based on the KPIC classification. Overall, 101 patients took CMs for a related risk factor: 64 for HTN, 36 for type 2 DM, 74 for HL, and 84 for antithrombotic purposes (Table 1). Furthermore, 56 patients took CMs for more than 2 risk factors; 37/64 patients with HTN and 24/36 with DM took multiple drugs, respectively (Fig. 2). Table 2 presents the CMs and KPIC classifications.

The patients also took CMs for other conditions, such as digestive system diseases (38%), mental/behavioral disorders
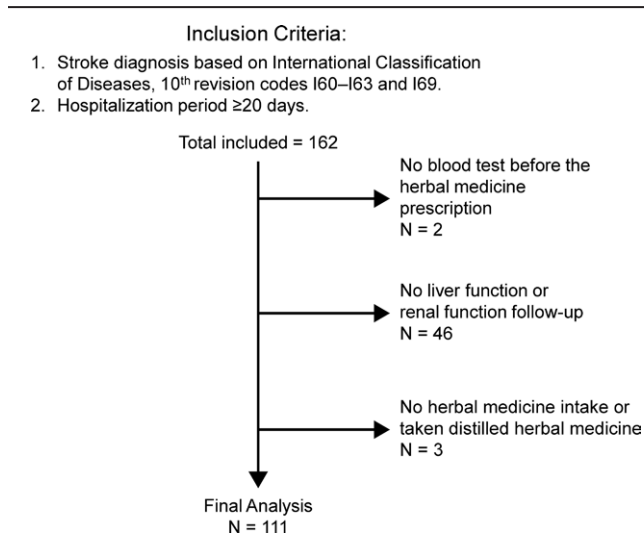
Table 1

Patient characteristics.

Characteristics	N
Number of patients	111
Male	53
Female	58
Mean age (years)	67.8
Mean hospitalization duration	72.6
Stroke types	
Cerebral infarction	81
Cerebral hemorrhage	30
CMs used for stroke risk factors	
HTN	64
DM	36
HL	74
HTN + DM	6
HTN + HL	24
DM + HL	9
HTN + DM + HL	17

CM = conventional medicine, DM = diabetes mellitus, HL = hyperlipidemia, HTN = hypertension.

Table 2

Korea Pharmaceutical Information Center medication classifications.

Characteristics	N
HTN medication	64
ARB	8
CCB (DHP)	14
CCB (NDHP)	1
ARB + CCB (DHP)	19
ARB + CCB (DHP) + hydrochlorothiazide	2
ARB + CCB (DHP) + chlorothalidone	1
BB	4
ARB + CCB (NDHP) + BB	1
ARB + CCB (DHP) + BB	4
ARB + CCB (DHP) + hydrochlorothiazide	2
ARB + CCB (DHP) + hydrochlorothiazide + furosemide	1
ARB + BB	2
CCB (DHP) + BB	3
ARB + hydrochlorothiazide	1
CCB (DHP) + hydrochlorothiazide	1
DM medication	36
Biguanide	6
Sufonylurea	2
DPP-4 inhibitor	3
Biguanide + DPP-4 inhibitor	11
Biguanide + sulfonylurea	3
Biguanide + sulfonylurea + DPP-4 inhibitor	4
DPP-4 inhibitor + TZD	2
Biguanide + SGLT-2 inhibitor + sulfonylurea	1
DPP-4 inhibitor + sulfonylurea	1
Biguanide + DPP-4 inhibitor + insulin	1
DPP-4 inhibitor + meglitinide + insulin	1
Insulin	1
HL medication	74
HMG-CoA reductase inhibitor	66
HMG-CoA reductase inhibitor + Ezetimibe	6
Fibrate	2
Antithrombotic medication	84
Aspirin	25
Clopidogrel	12
Cilostazol	3
Aspirin + clopidogrel	30
Aspirin + cilostazol	4
Aspirin + clopidogrel + cilostazol	1
Cilostazol + ticlopidine	1
Aspirin + ticlopidine	2
Apixaban	4
Rivaroxaban	1
Warfarin	1

ARB = angiotensin II receptor blocker, BB = beta blocker, CCB = calcium channel blocker, DM = diabetes mellitus, DPP-4 = dipeptidyl Peptidase-4, DHP = dehydropyridine, HL = hyperlipidemia, HMG-CoA = 3-hydroxy-methyl glutaryl-coenzyme A, HTN = hypertension, NDHP = non-dehydropyridine, SGLT-2 = sodium glucose cotransporter-2, TZD = thiazolidinedione.

(33%), and neurological disorders (11%; Fig. 3). Additionally, CMs were taken for circulatory and urinary system diseases, and short-term painkillers and antibiotics were administered if necessary.

3.3. HM use

HMs were prescribed as hot water extracts (N = 95) or pills (N = 2). Guibi-tang was the most common, followed by Yukmijihwang-tang, Gwibiondam-tang, Sunkihwalhyul-tang, and Jaeumgeonbi-tang. Gongjindan and Uhwangcheongsimhwan were administered as pills once daily in addition to other HMs in 10 cases each (Fig. 4).

3.4. Liver test abnormalities and injury

Liver test abnormalities were observed in 36 of 111 cases. Among them, 12 patients had an abnormal result in the initial test but returned to the normal range after simultaneously taking HMs and CMs. Furthermore, 17 patients had initial liver test abnormalities that remained but did not worsen after prescribing HMs (Table 3).

Contrastingly, 7 patients had normal results in the initial test but showed liver test abnormalities after taking CMs and HMs simultaneously. In 2 patients, ALT increase were within 2 times the ULN and recovered without stopping CMs or HMs. The other 2 patients showed a slight increase in ALT within 50% of ULN at the end of the hospitalization period (89 and 105 days each), but the follow-up test was absent. The other 2 patients showed ALT increase more than 2 times the ULN after simultaneously taking CMs and HMs. The possible causative drug was Seogyeong-tang (RUCAM scale = 3 points) and atorvastatin (RUCAM scale = 5 points) in patients 1 and 2, respectively (Table 4).

Liver injury was observed in only 1 patient, even in the initial test, after which the patient recovered after receiving HMs.

3.5. Renal function abnormalities and injury

None of the patients developed AKI. Five patients had renal function abnormalities; 4 had abnormal results on the initial test. After prescribing HM, 2 patients recovered and remained within the normal range, and 2 had renal abnormalities that remained but did not worsen. The last patient had normal test results initially but experienced renal function deterioration while simultaneously taking CMs and HMs. However, they did not meet the Kidney Disease Improving Global Outcomes criteria (Table 5).

4. Discussion

Globally, stroke is a major cause of mortality and disability. Once the "golden time" for applying tissue-plasminogen activators has passed, very little can be done to treat strokes.[6] Therefore, patients with stroke are often dissatisfied with their progress and seek complementary or alternative interventions, such as HMs.[7]
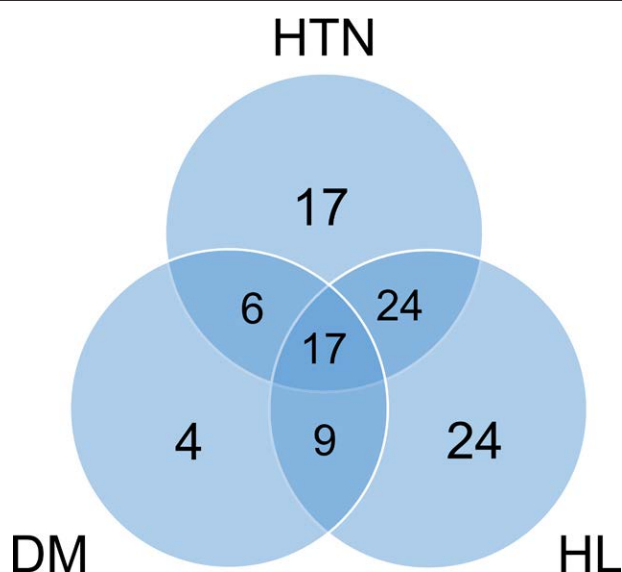
Figure 2. Conventional medicines taken for stroke risk factors. DM = diabetes mellitus, HL = hyperlipidemia, HTN = hypertension.

Evidence supporting alternative medicine is growing, and many researchers are investigating the effectiveness of HMs for treating stroke. For example, Wei et al reviewed 71 randomized controlled trials comprising 5770 patients on the potential efficacy of HM for improving neurological deficits after a stroke.[8] Venketasubramanian also commented on a meta-analysis of HMs for ischemic stroke, showing marked improvement in neurological deficits.[7] Moreover, mechanistic studies on the therapeutic effects of HMs are also being conducted. Zimmerman and Yarnell reported that HMs might be a new and effective way to prevent and treat ischemia and hemorrhagic stroke.[6] Furthermore, Gaire introduced a potential HM treatment mechanism for ischemic stroke.[9]

Stroke is a disease with sequelae and a high recurrence risk. Therefore, CMs that address stroke-related risk factors are generally administered throughout the patient's life. Similarly, long-term administration of HMs may be used for stroke treatment. Accordingly, HM-induced hepatotoxicity and nephrotoxicity concerns have been raised. For instance, Suk et al suggested that DILI is a highly relevant health problem in Korea, and HMs are the most common cause of DILI.[10] Furthermore, Touiti et al reported that HMs presented an actual risk to the kidney,[11] and Yang et al reviewed several causes of kidney damage from HMs.[12]

Generally, patients with stroke are older and take several CMs, increasing the possibility of hepatotoxicity and nephrotoxicity from multidrug interactions when combined with long-term HM use; these events may lead to a poor prognosis. Additionally, components extracted from herbs, such as aristolochic acids and other plant alkaloids, anthraquinones, flavonoids, and glycosides, appear to cause nephrotoxicity. Other factors may also contribute to the nephrotoxicity of HMs, such as the intrinsic toxicity of herbs, improper processing or storage, heavy metal content, overdoses, and interactions between HMs and CMs.[12] Therefore, this study investigated hepatotoxicity and nephrotoxicity in patients with stroke who took HMs and multiple CMs.

Overall, 1 of 111 patients showed liver injury, even in the initial test and recovered after taking HMs. Therefore, no liver injury due to the combination of HMs and CMs was observed in this study.

This result was based on the updated RUCAM score. However, patients should be closely monitored since aging and polypharmacy tend to increase the risk of hepatic and renal disorder.[13] Several studies have also show that liver disease and AKI are associated with poorer outcomes in stroke.[14,15] Therefore, its prevention is essential. In this study, the authors substituted patients with ALT level 2 times the ULN (unfit for liver injury criteria) with the RUCAM score to identify CMs or HMs that potentially cause liver injury. Based on the RUCAM score, Seogyeong-tang and atorvastatin were the causative drugs, with scores of 3 and 5, respectively. Similarly, the RUCAM score was also low because of the retrospective design of this study; however, this occurrence is consistent with previous studies. Atorvastatin therapy is associated with mild, asymptomatic, and usually transient serum aspartate transaminase elevations in 1% to 3% of patients; however, <1% of patients experience levels more than 3 times the ULN.[16] However, in the case of Seogyeong-tang, since no studies or case reports are available on the cause of elevated liver tests or liver injury, further studies are needed.

Woo et al reported a low prevalence of HM-induced liver injury,[17] and Cho et al reported an approximately 0.60% risk of HILI for inpatients, predominantly in women with a specific hepatocellular type.[18] Furthermore, Melchart et al reported that 26 of 21,470 patients (0.12%) treated with HM had liver injuries, which resolved shortly after treatment cessation.[19] Moreover, safety studies in specific disease groups are being conducted. For instance, Lee et al reported that the liver injury prevalence was low in patients with normal liver tests taking HMs for musculoskeletal treatment, and HM did not aggravate liver injury in most patients with injury before beginning the HM treatment.[2] Lee et al also reported that if HMs are appropriately prescribed by experts, combining them with CMs is safe and does not damage the liver and kidneys in patients with stroke.[20]

Conversely, some studies report the hepatotoxicity of HMs using the RUCAM score in Korea, but the number is limited, and the reliability is low. Ha et al conducted a systematic review of the Korean literature to determine the effect of HMs on liver function.[21] One randomized controlled trial, 1-panel study, 3 prospective studies, 4 retrospective studies, and 4 case reports were included. Among these, 1 retrospective study and 3 case reports suggested the possibility of HILI, but only 2 used the RUCAM score. Two studies that did not use the RUCAM score reported the possibility of liver injury caused by *Scutellaria Radix*[22] and Gamiyukgunja-tang,[23] respectively. Regarding studies using the RUCAM score, Jung et al reported that among 28 patients with *Dictamnus dasycarpus*-induced liver injury, 1 patient received a definitive score of 9 on the RUCAM score, and 27 patients with a probable score between 6 and 8.[24] Bae et al reported liver damage caused by *Polygoni Multiflori* on a RUCAM score of 10 (definitive).[25]

Table 3

Liver test abnormality and injury classifications.

Observation period	Liver test types	N
Initial	AST/ALT	11
	AST/ALT + ALP	0
	ALP	1
Initial and during CM + HM intake	AST/ALT	15
	AST/ALT + ALP	2
	ALP	0
During CM + HM intake	AST/ALT	6
	AST/ALT + ALP	0
	ALP	1
Liver injury	Initially	1
	During CM + HM	0

ALT = alanine transaminase, AST = aspartate transaminase, ALP = alkaline phosphatase, CM = conventional medicine, DB = direct bilirubin, HM = herbal medicine.
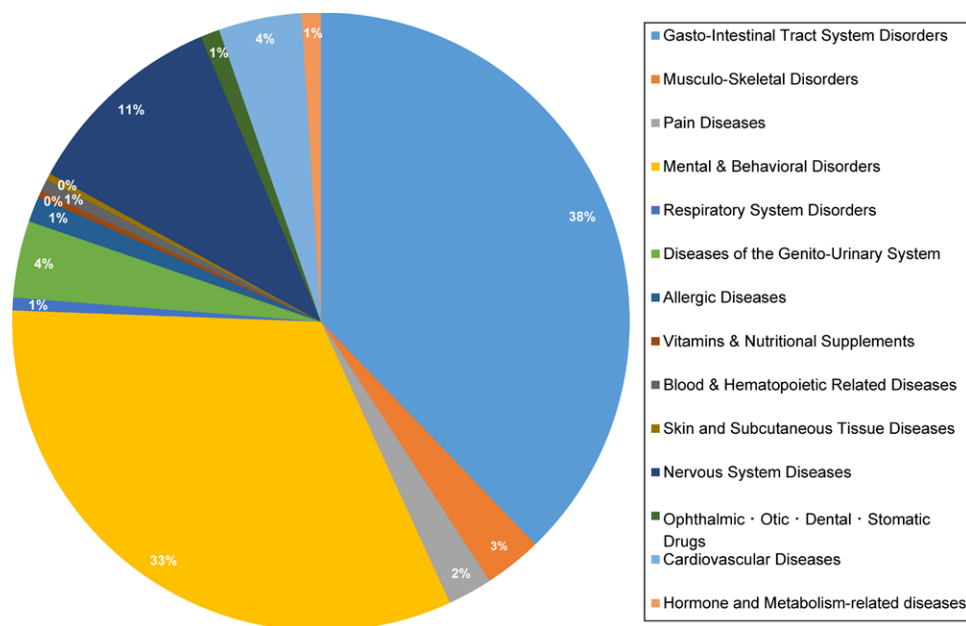
Figure 3. Conventional medicines used for conditions other than DM, HL, and HTN (stroke risk factors). DM = diabetes mellitus, HL = hyperlipidemia, HTN = hypertension.
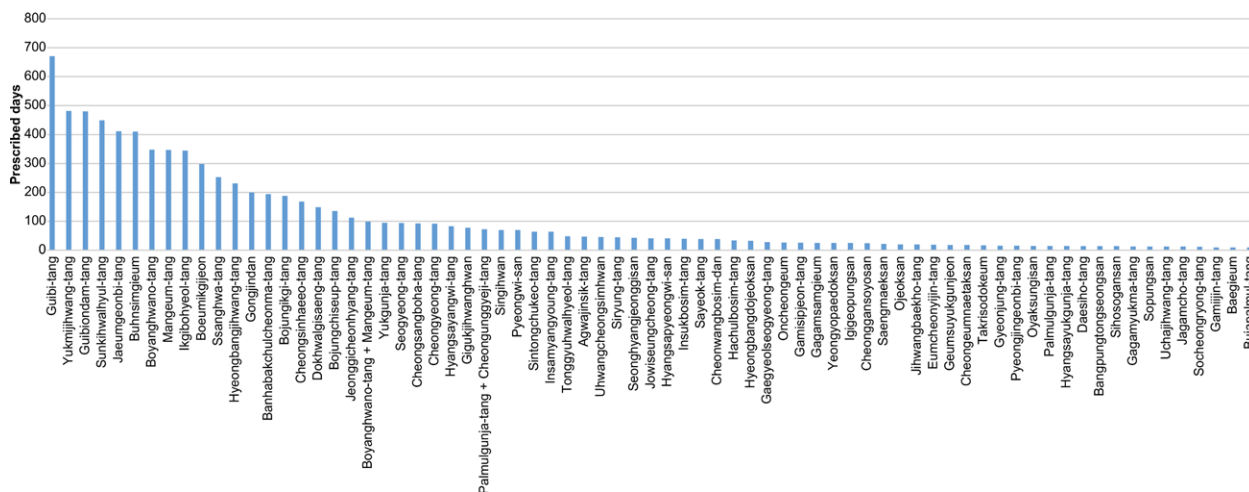

Figure 4. Frequently prescribed herbal medicines.

Using the RUCAM score for liver injury still requires development, and the number and scale of studies are lacking. However, considering the above results, the emphasis is on the method of administration rather than the HM. Korean medicine doctors prescribed the results that reported low hepatotoxicity. In studies reporting the hepatotoxicity of HM (*Dictamnus dasycarpus* and *Polygoni Multiflori*), it is believed that patients consumed HM as a health-functional food regardless of the prescription. However, the definition of HM must be determined first since not all herbs and health-functional foods can be defined as "Herbal Medicine." In Korea, this is specified through the Korean Herbal Pharmacopoeia, and the toxicity test and the processing method are stipulated and are being standardized.[26]

Here, none of the patients developed AKI, supporting previous studies, which reported that HMs did not affect renal function in patients with stroke. Furthermore, in this study, interactions between HMs and CMs frequently prescribed to patients with stroke, did not cause liver or renal injury. Similarly, these results differ from previous studies that raised concerns about hepatotoxicity and nephrotoxicity because the HM category varied per study. Lee et al found that in reports of HM-induced nephrotoxicity, aristolochic acid contained in *Aristolochia manshuriensis* and *A. fangchi* caused the nephropathy. However, in Korea, *Akebia quinata* and *Stephania tetrandra* are the plants mainly used as HMs.[27]

Korea has a dual medical system and has experts in HM toxicology, herb processing methods, HM dosing, quality control methods, and distribution. Therefore, in Korea, the hepatotoxicity and nephrotoxicity risks are minimal because specialized HMs are prescribed. Furthermore, the treatment also follows the Clinical Practice Guideline of Korean Medicine for Stroke.[28] Consequently, since new information and potential concerns emerge, it is crucial to share clinical experiences with HM treatments for patients with stroke and train HM specialists to minimize worries and provide optimal treatment.

Table 4

Liver injury analyses using the RUCAM scale.

Patients (gender/ age)	Hospitalization period (days)	Stroke type	Days to injury	Liver function test					HMs	Probable cause drug	RUCAM scale
P1 (F/50)	44	Hemorrhage	17		AST	ALT	ALP	GGT	Jaeumgeonbi-tang, Socheongryong-tang, Mangeum-tang, Seogyeong-tang	Seogyeong-tang	3 (Possible)
				2018.01.24	21.0	17.0	60.0	–			
				2018.02.26	44.0	86.0	56.0	44.0			
				2018.03.03	15.0	44.0	–	39.0			
	CMs			Losartan potassium 50 mg, Felodipine 5 mg, Rosuvastatin Calcium 10.4 mg, Acetyl-L-Carnitine Hydrochloride 590 mg, Ursodeoxycholic Acid 100 mg, Loxoprofen Sodium Hydrate 68.1 mg, Aceclofenac 100 mg							
P2 (F/74)	116	Infarction	23		AST	ALT	ALP	GGT	Boyanghwano-tang, Jaeumgeonbi-tang, Hyeongbangjihwang-tang, Ssanghwa-tang, Mangeum-tang, Gaegyeolseogyeong-tang, Tonggyuhwalhyeol-tang	Atorvastatin	5 (Possible)
				2016.11.23	54	56	101	146			
				2016.11.26	39	50	–	42			
				2016.12.06	28	21	–	32			
				2016.12.19	43	41	159	41			
				2016.12.27	63	84	–	54			
				2016.12.30	70	100	–	54			
				2017.01.02	40	44	–	47			
				2017.01.05	34	39	–	44			
				2017.01.12	31	37	–	37			
				2017.01.19	34	38	84	–			
				2017.02.15	35	47	107	42			
				2017.02.20	26	32	–	38			
				2017.03.06	22	35	–	34			
	CMs			Cilostazol 50 mg, Aspirin Enteric Gr. 120.98 mg, Ginkgo Leaf Ext. 80 mg, Ticlopidine HCl 250 mg, Atorvastatin Calcium 86.76 mg, Atorvastatin Calcium 43.4 mg, Pravastatin Sodium 40 mg, Ursodeoxycholic Acid 100 mg, Ursodeoxycholic Acid 100 mg, Choline Alfoscerate 400 mg, Itopride HCl 50 mg, Carbidopa 27 mg, Levodopa 100 mg, Ranitidine HCl 84 mg, Sucralfate 300 mg, Tripotassium Bismuth							

ALT = alanine transaminase, AST = aspartate transaminase, ALP = alkaline phosphatase, CM = conventional medicine, GGT = gamma-glutamyl transpeptidase, HM = herbal medicine, RUCAM = Roussel Uclaf Causality Assessment Method.

4.1. Limitations

This study had some limitations. First, this was a retrospective chart review, which explains the low RUCAM scores because the data were likely incomplete; this was the most significant study limitation. Second, since the HMs and CMs were frequently changed based on the patient's symptoms, it was impossible to determine the exact cause of liver and kidney damage. Third, this study had a small sample size and was conducted at a single center, and generalizing these results should be done cautiously. Consequently, future, large-scale, multi-center prospective studies are required to facilitate the collection of complete case data that allow for high RUCAM scores to confirm these results. Additionally, parallel assessments of the effectiveness of individual HMs would be optimal.

5. Conclusions

This study evaluated HMs for treating polypharmacy patients with stroke at a single center. Guibi-tang was the most used HM, followed by Yukmijihwang-tang, Gwibiondam-tang, Sunkihwalhyul-tang, and Jaeumgeonbi-tang. However, none of the patients had a drug-induced liver injury, and 2 patients showed more than 2 times the ULN for liver test abnormalities,

possibly caused by Seogyeong-tang and atorvastatin, and nephrotoxicity did not occur. Therefore, prescribing HMs to polypharmacy patients with stroke is safe for the liver and kidneys. However, consulting HM experts and using Korea's dual medical system are important for optimal effectiveness and prevention of adverse events.

Author contributions

Conceptualization: JunSeok Kim, WooSeok Jang.
Data curation: Junseok Kim.
Formal analysis: Junseok Kim.
Methodology: JunSeok Kim, WooSeok Jang.
Investigation: JunSeok Kim.
Supervision: WoosSeok Jang.
Validation: WooSseok Jang.
Writing- Original draft: JunSeok Kim.
Writing- review & editing: JunSeok Kim, WooSeok Jang.

Table 5

Renal function abnormality classifications.

Observation period	Renal function types	N
Initial	Creatinine	2
Initial and during CM + HM intake	Creatinine	2
During CM + HM intake	Creatinine	1

CM = conventional medicine, HM = herbal medicine.

References

[1] Korea Ministry of Health and Welfare. Survey data on the use of Herbal medicine. Available at: https://koms.or.kr/page/research-result/reality-people.do?menu_no=14. [access date July 08, 2022]. Published 2020.
[2] Lee J, Shin JS, Kim MR, et al. Liver enzyme abnormalities in taking traditional herbal medicine in Korea: a retrospective large sample cohort study of musculoskeletal disorder patients. J Ethnopharmacol. 2015;169:407–412.
[3] Park SU, Cho SY, Park JM, et al. Integrative treatment modalities for stoke victims in Korea. Complement Ther Clin Pract. 2014;20:37–41.

[4] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2016;17:14.

[5] Kellum JA, Lameire N, Aspelin P, et al. KDIGO-2012-AKI-Guideline-English. Kidney Int Suppl. 2012;2:1–138.

[6] Zimmerman C, Yarnell E. Herbal medicine for stroke. Altern Complement Ther. 2018;24:232–9.

[7] Venketasubramanian N. Complementary and alternative interventions for stroke recovery – a narrative overview of the published evidence. J Complement Integr Med. 2021;18:553–9.

[8] Wei M, Wang D, Kang D, et al. Overview of Cochrane reviews on Chinese herbal medicine for stroke. Integr Med Res. 2020;9:5–9.

[9] Gaire BP. Herbal medicine in ischemic stroke: challenges and prospective. Chin J Integr Med. 2018;24:243–6.

[10] Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol. 2012;107:1380–7.

[11] Touiti N, Houssaini TS, Achour S. Overview on pharmacovigilance of nephrotoxic herbal medicines used worldwide. Clin Phytosci. 2021;7:9.

[12] Yang B, Xie Y, Guo M, et al. Nephrotoxicity and Chinese herbal medicine. Clin J Am Soc Nephrol. 2018;13:1605–11.

[13] Abe J, Umetsu R, Uranishi H, et al. Analysis of polypharmacy effects in older patients using Japanese adverse drug event report database. PLoS One. 2017;12:e0190102.

[14] Tsagalis G, Akrivos T, Alevizaki M, et al. Long-term prognosis of acute kidney injury after first acute stroke. Clin J Am Soc Nephrol. 2009;4:616–22.

[15] Parikh NS, Merkler AE, Schneider Y, et al. Discharge disposition after stroke in patients with liver disease. Stroke. 2017;48:476–8.

[16] Atorvastatin. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. 2012. Atorvastatin. [Updated Dec 1, 2021].

[17] Woo HJ, Kim HY, Choi ES, et al. Drug-induced liver injury: a 2-year retrospective study of 1169 hospitalized patients in a single medical center. Phytomedicine. 2015;22:1201–5.

[18] Cho JH, Oh DS, Hong SH, et al. A nationwide study of the incidence rate of herb-induced liver injury in Korea. Arch Toxicol. 2017;91:4009–15.

[19] Melchart D, Hager S, Albrecht S, et al. Herbal traditional Chinese medicine and suspected liver injury: a prospective study. World J Hepatol. 2017;9:1141–57.

[20] Lee SH, Kim SY, Yang SB, et al. Safety of co-administration of herbal and conventional medicines on liver and kidney function in stroke patients: a single-center retrospective study. Phytomedicine. 2021;81:153435.

[21] Ha DJ, Je YR, Kim KL, et al. The effect of herbal medicine on liver function: a systematic review of the Korean literature. Int Korean Med. 2020;41:933–46.

[22] Lee KH, Yang JE, Chang GT. A psoriasis case report on liver damage related to Scutellaria Radix. J Korea Oriental Med. 2011;23:149–58.

[23] Shin WJ, Kim TY, Park Y, et al. One case of drug-induced liver injury after taking Gamiyukgunja-tang. Korean J Orient Int Med. 2011;32:444–50.

[24] Jung JH, Kim SH, Ko KH, et al. Clinical features of 28 acutely toxic hepatitis patients who ingested Dictamnus dasycarpus: a single center clinical experience. Int Korean Med. 2010;78:457–65.

[25] Bae SH, Kim DH, Bae YS, et al. Toxic hepatitis associated with Polygoni multiflori. The Korean J Hepatol. 2010;16:182–6.

[26] Kim TY, Kim DU, Kang YM. New insight of the needs for standardization on the processing of herbal medicines: concentrated on standard terminology. Korean Herb Med Inf. 2019;7:41–69.

[27] Lee B, Choi KL, Lee JS, et al. Is the term of Chinese herb nephropathy proper? Korean J Orient Intern Med. 2000;21:543–8.

[28] The Society of Stroke on Korean Medicine. Clinical practice guideline of Korean medicine. Seoul, Korea: NIKOM. 2021. Availabe at: NCKM; https://nikom.or.kr/nckm/module/practiceGuide/index.do?menu_idx=14. Published 2021.