Tropical Journal of Pharmaceutical Research November 2024; 23 (11): 1865-1971
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i11.9

Original Research Article

A retrospective study on modified Saireito for cancer patients with renal insufficiency

Sunkyu Choi[1], Jee Young Lee[2], En Hyung Kim[3,4], Shin Seong[5], Hanbing Li[6]*, Wonnam Kim[7]*

[1]Cnh Center for Cancer Research, Gangnam-gu, Seoul 06154, [2]Integrative Cancer Center, Cha Ilsan Medical Center, Goyang-si, Gyeonggi-do 10414, [3]Department of Dermatology, College of Medicine, Chungbuk National University, Cheongju, Chungbuk 28644, [4]Department of Dermatology, Chungbuk National University Hospital, Cheongju, Chungbuk 28644, [5]Soram Korean Medicine Hospital, Gangnam-gu, Seoul 06154, Republic of Korea, [6]Institute of Pharmacology, Department of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China, [7]Division of Pharmacology, School of Korean Medicine, Pusan National University, Yangsan, Gyeongnam 50612, Republic of Korea

For correspondence:* ***Email:* *eb75lab@pusan.ac.kr, hanniballee@zjut.edu.cn;* ***Tel:*** *+82-515108460*

Sent for review: 12 June 2024 *Revised accepted: 2 November 2024*

Abstract

Purpose: *To investigate the impact of Haejongdan (HJD), a modified Saireito, on the recovery of renal function in cancer patients.*

Methods: *This retrospective study was conducted using data from Soram Korean Medicine Hospital, Gangnam-gu, Seoul, Korea. A total of 166 patients with gastrointestinal, lung, breast, ovarian, thyroid and other cancers, who orally received HJD (5 g twice daily) between December 2019 and February 2021, were divided into normal kidney function (n = 120) and reduced kidney function (n = 46) groups. Comparisons were done based on the estimated glomerular filtration rate (eGFR) under 90 mL/min/1.73 m^2. Glomerular filtration rate was estimated using CKD Epidemiology Collaboration equation (eGFR). Blood urea nitrogen (BUN), creatinine, high-sensitivity C-reactive protein (hs-CRP) and chlorine levels were also determined.*

Results: *Participants in the reduced kidney function group were older and had a higher baseline creatinine, BUN, chlorine and lower eGFR. The 6-month follow-up evaluation of renal function-related factors showed that most of the improvement in eGFR occurred in the reduced kidney function group. However, in normal kidney function group, eGFR trend was significantly unchanged throughout the study. In the reduced kidney function group, eGFR slope decreased before receiving HJD and increased significantly ($p \leq 0.0001$) after receiving HJD. The hs-CRP level showed a decreasing tendency after receiving HJD ($p = 0.0005$).*

Conclusion: *Haejongdan has some potential to prevent nephrotoxicity in patients with cancer, especially those who have Renal insufficiency (RI). Further randomized, controlled study is necessary to confirm the results.*

Keywords: *Renal insufficiency, Chemotherapy, Nephrotoxicity, Estimated glomerular filtration rate, High sensitivity C-reactive protein, Saireito*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Cases of cancer patients with renal insufficiency (RI) are frequently encountered in clinical practice [1]. Several studies have reported the association between RI and the reduction in overall survival rate and an increase in cancer death rate [2]. This is an important issue when managing cancer patients using chemotherapeutic drugs. About half of all anticancer drugs are mainly excreted unchanged or as metabolites in the urine [3]. Thus, any decline in renal clearance may lead to an overdose and potentially toxic accumulation. In addition, studies have suggested that apoptosis, necrosis, oxidative stress and inflammation in the proximal tubules and collecting ducts are involved in cisplatin-induced renal injury [4].

Saireito (*Siryung-tang* in Korea, *Chai-ling-tang* in China), a herbal mixture, is composed of the following 12 plants viz *Bupleurum falcatum*, *Alisma orientale*, *Atractylodes macrocephala*, *Polyporus umbellatus*, *Poria cocos*, *Pinellia ternata*, *Scutellaria baicalensis*, *Panax ginseng*, *Glycyrrhiza glabra*, *Cinnamomum cassia*, *Zizyphus jujuba* and *Zingiber officinale* [5]. *Saireito* has been used to treat edema, diarrhea, nephritis, and gastroenteritis [6,7]. In addition, reports have shown the pharmacological functions of *Saireito* to include anti-inflammatory and anti-fibrotic effects [7]. *Haejongdan* (HJD) is a modified version of *Saireito* lacking two components viz *Zizyphus jujuba* and *Zingiber officinale*. In this study, the impact of HJD on the recovery of renal function in cancer patients was investigated.

METHODS

Study population

This retrospective study was performed at Soram Korean Medicine Hospital, Seoul, Korea. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki [8] and was approved by Korean Public Institutional Review Board (approval no. P01-202110-21-002). All cancer patients who orally received 5 g of HJD twice per day, on average, between 1 December 2019 and 28 February 2021, were screened for inclusion. The exclusion criteria were as follows: patients with renal failure; and patients who did not determine their creatinine levels more than twice within the study period.

Finally, a total of 166 subjects with gastrointestinal, lung, breast, ovarian, thyroid and other cancer types were included. The patients were divided into normal kidney function (n = 120) and reduced kidney function (n = 46) groups and comparisons were done based on the estimated glomerular filtration rate (eGFR) under 90 mL/min/1.73 m^2.

Renal function-related factors

Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eqs 1 - 4.

For women, if serum creatinine (Scr) ≤ 0.7: $eGFR = 144(Scr/0.7)^{-0.329} \times 0.993^{Age}$ …… (1)

if Scr > 0.7: $eGFR = 144(Scr/0.7)^{-1.209} \times 0.993^{Age}$ …….. (2)

For men, if Scr ≤ 0.9: $eGFR = 144 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$ …… (3)

if Scr > 0.9: $eGFR = 144(Scr/0.9)^{-1.209} \times 0.993^{Age}$ …… (4)

where the unit of serum creatinine is in mg/dL [9]. Serum BUN and hs-CRP levels were also determined at follow-up.

Statistical analysis

The patients' characteristics and number of events are presented as the mean ± standard deviation (SD) or numbers (%). The continuous variables were compared using *t*-test and categorical variables were compared using Chi-square (χ^2) test or Fisher's exact test as appropriate. The generalized estimating equation (GEE) was used to estimate the changes in renal functions over time after taking HJD [10].

The difference in the renal function slope trajectory between the normal kidney function group and the reduced kidney function group was also tested by GEE. The mean and confidence interval over time were compared to evaluate the trend of renal functions within each group using graphical representation. As subgroup analysis, a piecewise linear mixed-effects was used to verify the changing trend of eGFR and hs-CRP in the group that received HJD and the reduced kidney function group [11]. Paired *t*-test was performed to determine significant differences of eGFR and hs-CRP between baseline and after 2 months.

A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using R statistical software package (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of study participants

Table 1 shows the characteristics of the participants according to their kidney function. A total of 166 patients were enrolled comprising 46 patients (27.7 %) with reduced kidney function and 120 patients (72.3 %) with normal kidney function. The average age at the time of receiving HJD was 49.9 ± 9.9 years. Participants in the reduced kidney function group tended to have older age and higher baseline creatinine, BUN, chlorine and lower eGFR. Sex, patient history of diabetes or hypertension and other blood test results were not significantly ($p > 0.05$) different between the two groups. Chronic Kidney Disease (CKD) stage was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) GFR classification [12]. The normal kidney function group showed a higher rate of breast cancer (56.7 % vs 30.4 %, $P = 0.004$) but there was no significant difference in other cancer types.

Trend analysis of renal function-related factors

The generalized estimating equation (GEE) linear regression modeling was performed to estimate the slope difference of renal function-related factors after receiving HJD between the two kidney function groups (Table 2). Model 1 was adjusted for only baseline difference in eGFR, creatinine, BUN and hs-CRP between the two groups as appropriate. Additionally, Model 2 was adjusted for age, sex, diabetes and hypertension (systolic blood pressure). Furthermore, the estimated unadjusted and adjusted eGFR trajectory slopes in reduced kidney function group during the study period were significantly greater than the increase per day in the normal kidney function group (unadjusted $p = 0.0101$, adjusted $p = 0.0322$). Also, the estimated unadjusted and adjusted creatinine decline slope differences between the two groups were significant (unadjusted $p = 0.0193$, adjusted $p = 0.0246$).

Table 1: Baseline characteristics of the study participants

Characteristic	Total (n = 166)	Reduced kidney function group (n = 46)	Normal kidney function group (n = 120)	*P*-value
Age, year	49.9±9.9	57.1±8.7	47.2±8.9	<0.001
Sex				
Male	14(8.4)	6(13.0)	8(6.7)	0.312
Female	152(91.6)	40(87.0)	112(93.3)	
Diabetes	94(56.0)	27 (58.7)	66(55.0)	0.799
Hypertension	69(41.6)	21(45.7)	48(40.0)	0.627
SBP (mmHg)	113.5±12.4	112.0±12.3	114.0±12.4	0.343
Hemoglobin (g/dL)	11.5±1.5	11.5±1.5	11.5±1.5	0.729
Albumin (g/dL)	4.2±0.5	4.3±0.5	4.3±0.5	0.613
hs-CRP (mg/dL)	0.7±2.5	1.2±3.7	0.5±1.8	0.238
eGFR (mL/min/1.73m^2)	98.1±15.3	79.2±11.0	105.3±9.3	<0.001
Creatinine (mg/dL)	0.7±0.2	0.9±0.2	0.7±0.1	<0.001
BUN (mg/dL)	14.1±4.5	16.3±4.9	13.3±4.0	<0.001
Chlorine (mmol/L)	104.9±2.8	105.6±2.3	104.6±3.0	0.064
Sodium (mmol/L)	140.9±2.8	141.3±2.2	140.8±3.1	0.275
Potassium (mmol/L)	4.2±0.4	4.3±0.4	4.1±0.5	0.107
Phosphorus (mg/dL)	3.8±0.6	3.8±0.6	3.8±0.6	0.958
CKD stage				***<0.001***
1	120(72.5)	0	120(100)	
2	43(25.7)	43(93.5)	0	
3A	1(0.6)	1(2.2)	0	
3B	2(1.2)	2(4.3)	0	
Cancer type*				
Gastrointestinal	21(12.6)	9(19.6)	12(9.9)	0.156
Lung	13(7.8)	6(13.0)	7(5.8)	0.221
Breast	82(49.4)	14(30.4)	68(56.7)	0.004
Ovarian	18(10.8)	8(17.4)	10(8.3)	0.161
Thyroid	15(9.0)	4(8.7)	11(9.2)	0.999
Others	27(16.3)	8(17.4)	19(15.8)	0.993

Note: Values are presented as either mean ± standard deviation (SD) or numbers (percentage). SBP: systolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; CKD: chronic kidney disease. * Including patients with multiple tumors

On the other hand, the differences in trends of BUN over time were not significant in both unadjusted and adjusted slopes (unadjusted $p = 0.1566$, adjusted $p = 0.4674$) while the estimated

unadjusted slope difference of hs-CRP was significantly different though the adjusted slope difference was not significant (unadjusted p = 0.0466, adjusted p = 0.4868).

The 6-month follow-up evaluation of renal function-related factors stratified by baseline level of eGFR is presented in Figure 1. The majority of improvement in eGFR occurred in the reduced kidney function group which was detected at 2-month follow-up and this remained stable. In the normal kidney function group, eGFR trend did not seem to change significantly over the whole period. The decline of creatinine was mostly noticed in reduced kidney function group and was similar to the increase in eGFR. The trajectory of BUN over time was stable in both groups. Furthermore, variations in hs-CRP levels in the reduced kidney function group were more unpredictable than in the normal kidney function group. The follow-up loss rate was 16.7 % at 2 months and 50.6 % at 6 months.

Reduced kidney function patient subgroup analysis

Regarding renal function, only eGFR and hs-CRP were abnormal in reducing the kidney function group. The recovery rate of the two factors after receiving HJD was investigated. The slope before and after HJD administration was estimated by piecewise linear mixed-effects model (Table 3). The eGFR slope was decreased before receiving HJD but then increased significantly ($p \leq 0.0001$) after administration of HJD. Also, the hs-CRP level showed a decreasing tendency after receiving HJD (p = 0.0005).

Table 2: Change slope in renal function-related factors between the two groups

Renal function related factor	Model 1			Model 2 (adjusted confounders*)		
	Coefficient	Standard error	*P*-value	Coefficient	Standard error	*P*-value
eGFR (mL/min/1.73m^2)	0.084	0.033	0.010	0.060	0.028	0.032
Creatinine (mg/dL)	−0.001	0.0002	0.019	−0.0004	0.0002	0.025
BUN (mg/dL)	−0.010	0.007	0.156	−0.005	0.007	0.467
hs-CRP (mg/dL)	0.006	0.003	0.047	0.004	0.005	0.487

Note: *Adjusted variables included age; sex, diabetes, hypertension, and systolic blood pressure

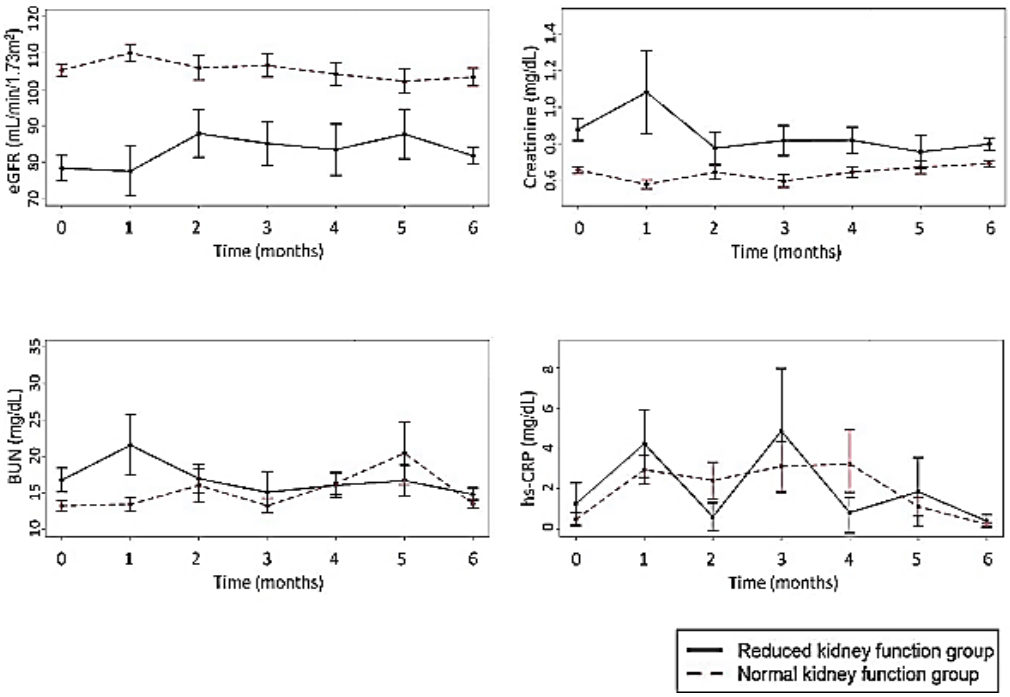

Figure 1: Summary plot of renal function-related factors trajectories over time divided by baseline eGFR. Data points represent mean and confidence intervals of renal function-related factors for each month

Table 3: Piecewise mixed-effect regression model predicting renal function intervention over time in reduced kidney function patients

Renal function	Baseline trend			Trend change after intervention		
	Coefficient	***Standard error***	***P-value***	***Coefficient***	***Standard error***	***P-value***
eGFR (mL/min/1.73m^2)	-0.541	0.105	<0.001	0.902	0.209	<0.001
hs-CRP (mg/dL)	0.151	0.057	0.008	-0.330	0.094	0.001

The boxplot of increment rate in eGFR and hs-CRP, 2 months after baseline, is shown in Figure 2. The median increment rate of eGFR was greater than 0 and hs-CRP was lower than 0. The differences of eGFR and hs-CRP between baseline and after 2 months were 10.63 (CI: 4.97, 17.4, p = 0.0008) and -0.61 (CI: -0.95, -0.26, p = 0.0010), respectively.

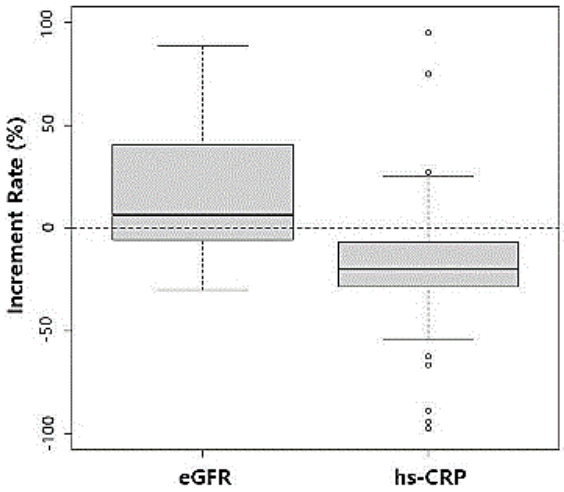

Figure 2: Boxplot indicating increment rate in eGFR and hs-CRP 2 months after baseline

DISCUSSION

Renal insufficiency is a common comorbidity in patients with cancer [13]. Geriatric patients with cancer experience a higher prevalence of RI than patients without cancer due to the tumor itself as well as the chemotherapeutic agents or other nephrotoxic agents in use [13]. A French national observational cohort study, also known as the renal insufficiency and cancer medication (IRMA) study, showed that 57.4 % of patients with solid tumors had abnormal renal function, 80.1 % of patients received potentially nephrotoxic drugs, and 53.4% of anticancer drug prescriptions required dose adjustments for RI [14]. In the present study, participants in the reduced kidney function group were older and had higher baseline creatinine, BUN, chlorine and lower eGFR compared to the normal kidney function group. Interestingly, patient history of diabetes or hypertension was not significant between the two groups. Also, other than breast cancer, no significant difference was seen in other cancer types. Considering the narrow therapeutic indexes of anticancer drugs, dose reduction and frequent dose adjustments may lead to under-dosing or life-threatening toxicity. The mechanism of nephrotoxicity is not fully revealed but inflammation has a key role in acute renal failure.

Cisplatin, one of the most frequently used platinum-based chemotherapeutic agents induces inflammation that triggers acute kidney injury via mitochondrial dysfunction and the subsequent cyclic GMP-AMP synthase (cGAS) stimulator of interferon genes (STING) pathway activation [15]. Most cancer patients may experience acute kidney injury due to some conditions or nephrotoxic agents. However, a significant number of patients who recovered from acute kidney injury progressed to end-stage renal disease [16]. Full doses of chemotherapeutic agents are recommended for patients with mild or subclinical RI and prophylactic medication is often used to prevent RI. Prophylactic use of N-acetylcysteine or sodium bicarbonate was widely used for contrast-induced nephropathy but was uncertain for chemotherapeutic agents including cisplatin [17]. Other potential renoprotective agents for chemotherapy were also studied but were not effective [18].

Saireito, a herbal mixture composed of 12 plants, is often used for diseases related to inflammation [5]. *Haejongdan* (HJD) is a modified version of *Saireito* lacking two components viz *Zizyphus jujuba* and *Zingiber officinale*. An *in vivo* study showed the renoprotective effect of *Saireito*, by ameliorating gentamicin-induced nephrotoxicity [19]. The antioxidant effect of *Saireito* is suggested to be mediated via reduction of urinary N-acetyl-beta-D-glucosaminidase and proteinuria, and increased creatinine clearance [19]. In this study, the eGFR trajectory slopes in the reduced kidney function group were significantly greater than the normal kidney function group per day increase. The creatinine decline slope differences between the two groups were also significant. Moreover, the evaluation of renal function-related factors by 6-month follow-up showed that the majority of improvement in eGFR occurred in the reduced kidney function group and improvement in eGFR was detected at 2-month follow-up. Also, the anti-inflammatory effect of *Saireito* against nephritic disease has been reported [20].

The estimation by piecewise linear mixed-effects model showed that after HJD treatment in the reduced kidney function group, eGFR and hs-CRP recovery rates were significant. Experimental study suggested that saikosaponin D, an active component in *Saireito*, showed anti-nephritic effect via glucocorticoid receptor stimulation [20]. *Saireito* and saikosaponin D both attenuated intraglomerular inflammation by suppressing IL-2 levels in a glomerulonephritis rat model [20]. The 7 herbal mixture, *Shosaikoto*, which is mostly included in HJD, had case reports about side effects such as interstitial pneumonia and acute respiratory failure [21]. However, specific side effects of *Shosaikoto* were not observed in Sprague Dawley rats up to doses of 2000 mg/kg for 13 weeks [22]. Also, there were two patients with intrahepatic bile duct carcinoma in the study population and no side effects were found in these patients after taking HJD for over a month.

Limitations of this study

This study is a retrospective single-arm study and it is possible that various confounding variables were included in the patients.

CONCLUSION

In patients with cancer, preserving renal function is important in preventing acute kidney injury or chronic renal failure and also in ensuring effective chemotherapeutic agents are used for the intended treatment time. *Haejongdan* (HJD) has the potential to prevent nephrotoxicity in patients with cancer, especially those who have RI. Further randomized, controlled study is necessary to confirm the results.

DECLARATIONS

Acknowledgements

None.

Funding

This work was supported by a 2-Year Research Grant from Pusan National University, Korea.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Korean Public Institutional Review Board (Seoul, Korea) (IRB-No: P01-202110-21-002; approval date: 06 October 2021).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Sunkyu Choi and Jee Young Lee are co-first authors. Sunkyu Choi, Hanbing Li, and Wonnam Kim conceived and designed the study. Sunkyu Choi and Jee Young Lee collected, analyzed and interpreted the experimental data. Sunkyu Choi, Jee Young Lee, En Hyung Kim, and Wonnam Kim drafted the manuscript. En Hyung Kim, Shin Seong, Hanbing Li, and Wonnam Kim revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. *Janus N, Launay-Vacher V, Byloos E, Machiels JP, Duck L, Kerger J, Wynendaele W, Canon JL, Lybaert W, Nortier J, et al. Cancer and renal insufficiency results of the BIRMA study. Br J Cancer 2010; 103(12): 1815-1821.*
2. *Launay-Vacher V, Janus N, Deray G. Renal insufficiency and cancer treatments. ESMO Open 2016; 1(4): e000091.*
3. *Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 2007; 43(1): 14-34.*

4. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007; 334(2): 115-124.
5. Kato S, Hayashi S, Kitahara Y, Nagasawa K, Aono H, Shibata J, Utsumi D, Amagase K, Kadowaki M. Saireito (TJ-114), a Japanese traditional herbal medicine, reduces 5-fluorouracil-induced intestinal mucositis in mice by inhibiting cytokine-mediated apoptosis in intestinal crypt cells. PLoS One 2015; 10(1): e0116213.
6. Hattori T, Maruyama H, Nishimura H, Nakai Y, Sakakibara I, Kase Y, Takeda S. Effects of Saireito, a Japanese herbal medicine, on edema via antagonistic actions against aldosterone in anti-GBM nephritic rats. Clin Exp Nephrol 2006; 10(1): 13-18.
7. Oyama M, Murata K, Ogata M, Fujita N, Takahashi R. Saireito improves lymphatic function and prevents UVB-induced acute inflammation and photodamage in HR-1 hairless mice. Evid Based Complem Alternat Med 2021; 2021: 3707058.
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.
9. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9): 604-612.
10. Leffondre K, Boucquemont J, Tripepi G, Stel VS, Heinze G, Dunkler D. Analysis of risk factors associated with renal function trajectory over time: a comparison of different statistical approaches. Nephrol Dial Transplant 2015; 30(8): 1237-1243.
11. Naumova EN, Must A, Laird NM. Tutorial in Biostatistics: Evaluating the impact of 'critical periods' in longitudinal studies of growth using piecewise mixed effects models. Int J Epidemiol 2001; 30(6): 1332-1341.
12. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3(1): 1-150.
13. Krens SD, Lassche G, Jansman FGA, Desar IME, Lankheet NAG, Burger DM, van Herpen CML, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20(4): e200-e207.
14. Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, Morere JF, Beuzeboc P, Deray G. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer 2007; 110(6): 1376-1384.
15. Maekawa H, Inoue T, Ouchi H, Jao TM, Inoue R, Nishi H, Fujii R, Ishidate F, Tanaka T, Tanaka Y, et al. Mitochondrial damage causes inflammation via cGAS-STING signaling in acute kidney injury. Cell Rep 2019; 29(5): 1261-1273 e1266.
16. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012; 81(5): 442-448.
17. Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med 2016; 164(6): 406-416.
18. Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, Cleton FJ, Osanto S. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomized, double-blind, placebo-controlled study. Eur J Cancer 2004; 40(11): 1713-1723.
19. Ohno I, Shibasaki T, Nakano H, Matsuda H, Matsumoto H, Misawa T, Ishimoto F, Sakai O. Effect of Sairei-to on gentamicin nephrotoxicity in rats. Arch Toxicol 1993; 67(2): 145-147.
20. Hattori T, Nishimura H, Kase Y, Takeda S. Saireito and saikosaponin D prevent urinary protein excretion via glucocorticoid receptor in adrenalectomized WKY rats with heterologous-phase anti-GBM nephritis. Nephron Physiol 2008; 109(2): 19-27.
21. Nishimori F, Yamazaki K, Jin Y, Yoshimura N, Tsukimoto K, Beppu H, Ichioka M, Yoshizawa Y. Pneumonitis induced by the drug ougon. Nihon Kokyuki Gakkai Zasshi 1999; 37(5): 396-400.
22. Lee MY, Seo CS, Shin IS, Kim YB, Kim JH, Shin HK. Evaluation of oral subchronic toxicity of soshiho-tang water extract: the traditional herbal formula in rats. Evid Based Complement Alternat Med 2013; 2013: 590181.