Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research Article

Herbal medicine use in Republic of Korea to alleviate side effects of COVID-19 vaccines: A cross-sectional study ☆

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) has spread worldwide, and several virus variants have emerged. Vaccines are administered to help prevent the infection. In Republic of Korea, most people take herbal medicine. This study investigated the use of herbal medicine to counter the side effects of COVID-19 vaccines.

Methods: This cross-sectional study was conducted using an online survey. Chi-square tests were used to determine differences in the use of herbal medication according to sociodemographic characteristics. Independent two-sample and paired *t*-tests were performed to examine the effect and satisfaction of herbal medicine use for countering the side effects of COVID-19 vaccines. One-way analysis of variance was used to determine vaccine-related differences.

Results: A total of 233 and 181 participants received the first and second doses of COVID-19 vaccines, respectively. The majority of herbal medicine users were in their thirties, had a bachelor's degree, suffered from side effects of vaccination, and received Vaxzevria for their first COVID-19 vaccine dose and Comirnaty for their second dose. The herbal medicine group had a higher satisfaction level of post-vaccination side effects than the non-herbal medicine group ($P < 0.0001$). The numeric rating scale scores for vaccination side effects were lower among participants who took herbal medication to alleviate those symptoms ($P < 0.0001$). The most commonly used herbal formula was Shuanghetang.

Conclusion: A third of participants receiving COVID-19 vaccines used herbal medication to counter the side effects of vaccination. The use of herbal medicine was associated with age, education level, vaccine brand, and whether side effects of vaccination occurred. Herbal medication use was associated with greater satisfaction compared to vaccine recipients not using herbal medication.

1. Introduction

Since coronavirus disease 2019 (COVID-19) was first recognized, several vaccines have been approved by the ministry of health (MOH) in each nation, such as Comirnaty (Pfizer Inc., NY, USA), Spikevax (Moderna Inc., MA, USA), Vaxzevria (AstraZeneca Public Limited Company, Cambridge, UK) and Ad26.COV2.S (Janssen Pharmaceuticals, Beerse, Belgium). Before prescription medicine was available for COVID-19, patients received symptomatic treatment according to guidelines such as those of the Korean Centers for Disease Control and Prevention [1]. Similar to other governments, the Republic of Korean government decided to focus on infection control by implementing various regulations including the quarantine of international travelers, restriction of business hours, and public vaccination. The vaccination program started on April 2021 for healthcare workers, aircrews, essential social workers, and patients with chronic diseases. When the side effects of vaccines became an issue, some vaccines were suspended, causing anxiety to the public, which led to an unmet goal for vaccination rates. As of April 22, 2021, 3.67% of the Republic of Korean population had received the first dose of the vaccine [2]. Those with mild side effects, including injection site pain, swelling or redness, slight fever, or headache, treated themselves with acetaminophen. By July 7, 2021, the vaccination rate had increased to 29.9% for the first dose and 10.6% for the second dose [2]. In December 2021, a new virus variant, Omicron, spread to Republic of Korea, and the MOH responded by reducing the dose interval from 6 months to 3 months [3]. This could have been the result of concerns about side effects, including both positive and negative unintended outcomes. The negative results, called adverse effects, are characterized by local and systemic reactions, such as redness,

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swelling, pain at the injection site, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain [4]. It is important to control the side effects of treatments because they impact the adherence of patients [5,6].

Concomitantly, in November 2020, the MOH started a demonstration project using herbal medicine (HM) under national health insurance (NHI); this took advantage of the increased use of HM in Republic of Korea, which was also occurring in other countries around the world [7,8], especially in the management of COVID-19 [9,10]. HM is defined as the medicine collected from animals, plants or minerals, including dried, cut, refined, or in its original form; previously, these medicines were prescribed only in boiled liquid or ground powder. However, currently HM are also available as soft extracts, tablets and capsules, enabling patients to take them more easily. This led to the increased usage of HM, which in turn raised the risk of adverse reactions [11]; therefore, regulating or restraining the use of HM became necessary for safety.

To the best of our knowledge, there is no guideline regarding the use of HM to treat the vaccine side effects. There have been four Korean studies since 2016 describing the side effects of vaccines [12–15]; but no study has reported on the use of HM with vaccines. Therefore, this study investigates the use of HM to counter the side effects of COVID-19 vaccines in Republic of Korea.

2. Material and methods

2.1. Participants

The target population was adults aged $\geq$ 18 years who had received at least one dose of a COVID-19 vaccine. Those who voluntarily agreed to participate in the study undertook an online survey. Recruitment was conducted through online advertisements in addition to a mailing to members of the Association of Public Health Doctors of Korean Medicine (APKOM) between August 27 and October 20, 2021. For requests to collect participants, the online advertisements including brief contents of the survey were posted on the websites and mails for doctors of Korean Medicine (KM).

2.2. Ethics

This study was approved by the Korea National Institute for Bioethics Policy, MOH (No. P01-202108-21-015) and was conducted in accordance with the *Declaration of Helsinki*. Written informed consent was obtained from all participants before completing the questionnaire.

2.3. Questionnaire

The questionnaire was designed to investigate the side effects of COVID-19 vaccinations and the use of HM, based on a previous study [16] that reported the side effects of vaccinations administered by the MOH. The side effects were represented by muscle pain, fever, headache, nausea, redness and the others. The questionnaire included 80 questions and was drafted by one physician who specialized in KM and was reviewed by five KM specialists. Participants were asked to answer a minimum of 16 questions regarding sociodemographic characteristics (gender, age, region and education level), health status, as well as information on the vaccination and their use of HM. Symptoms and satisfaction levels were quantified using the numeric rating scale (NRS) and a 5-point Likert scale. The questionnaire results had a content validity index of 0.87 with a Cronbach's α of 0.913 for symptom-related variables and 0.723 for satisfaction level.

2.4. Analysis

The sample size was calculated using G-power (version 3.1.9.7, Heinrich-Heine-Universität, Düsseldorf, Germany). It was conducted using an independent two-sample *t*-test (two-tailed, means, two groups; H1: 0.5; α-error: 0.05; power: 0.80; allocation ratio: 1) and paired *t*-test (two-tailed, means, matched pairs; H1: 0.5, α-error: 0.05; power: 0.80). One-way analysis of variance was also performed using fixed effects (one-way; H1: 0.5; α-error: 0.05; power: 0.8). The sample size was computed as 128, 34 and 48 during each analysis. The dropout rate was considered as 10%, and the minimum sample size was determined as 231.

This was a cross-sectional study based on the Strengthening the Reporting of Observational Studies in Epidemiology checklist [17]; therefore, the results were analyzed using descriptive statistics. All responses were collected using Google Forms (Google LLC, Mountain View, CA, USA) and Microsoft Excel 2010 (ver. 14.0, Microsoft, Redmond, WA, USA) and were analyzed using SAS (ver. 9.0, SAS Institute Inc., Cary, NC, USA).

Descriptive and inferential statistics were calculated using percentages (%), means, standard deviation (presented as mean ± standard deviation), medians, and interquartile range to present sociodemographic variables, symptom-related variables and satisfaction levels. Inferential statistics were performed using the chi-square test between HM (independent variable) and sociodemographic variables, types of vaccines, and symptom-related variables (dependent variables) to determine the difference in use of herbal medication according to sociodemographic characteristics. After checking for homogeneity of variance, the independent two-sample *t*-test between HM (independent variable) and symptom-related variables and satisfaction level (dependent variables), and the paired *t*-test for before and after HM use were performed to examine the effect of and satisfaction with HM to manage the side effects of COVID-19 vaccines. One-way analysis of variance (Kruskal-Wallis test) and post-hoc tests (Dwass, Steel, Critchlow-Filgner multiple comparison analysis) between types of vaccines (independent) and symptom-related variables (dependent) were performed to investigate vaccine side effects. If data were missing, they were excluded only for that participant. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Sociodemographic characteristics

A total of 233 participants were included in this study. All participants had received at least one dose of a COVID-19 vaccine, and 181 had received a second dose. The characteristics of HM users and non-HM users are detailed in Tables 1 and 2 for the first and second doses, respectively. Region was divided into capital area, including Seoul, Incheon and Gyeonggi-do, and non-capital area. Pre-existing conditions in the participants included hypertension (n = 6), diabetes (n = 3), cardiovascular disease (n = 2), atopic dermatitis (n = 2), cancer (n = 2), nephritis (n = 1) and others (n = 5). Among the participants who received two doses of vaccine, 72 received vaccine doses from different manufacturers. Only one changed from Comirnaty to Vaxzevria; the others changed from Vaxzevria to Comirnaty. All those who received Spikevax in the first dose received the same in the second dose.

3.2. Side effects of COVID-19 vaccinations

Of the total, 138 and 88 participants reported experiencing side effects from the first and second doses, respectively. Vaxzevria was administered as the first dose among most participants (73/138, 52.90%); however, Comirnaty was administered mostly for the sec-

Table 1
Sociodemographic characteristics of participants who received the first dose.

Item	Total (n = 233)	HM group (n = 85)	Non-HM group (n = 148)	P value
Gender				0.078
Male	65.24	72.41	61.07	
Female	34.76	27.59	38.93	
Age				< 0.0001
< 30 years	36.05	16.09	46.98	
30 s	33.48	49.43	23.49	
40 s	17.60	24.14	14.77	
50 s	9.87	10.34	10.07	
≥ 60 years	3.00	0.00	4.70	
Education level				< 0.0001
≤ High school	15.88	1.15	24.16	
Bachelor's degree	53.65	58.62	51.01	
Master's degree	16.31	14.94	13.42	
Doctor's degree	14.16	25.29	11.41	
Region				0.518
Capital area	51.93	54.02	49.66	
Non-capital area	48.07	45.98	50.34	
Underlying disease				0.057
Yes	9.01	4.60	12.08	
No	90.99	95.40	87.92	
Vaccine brand				< 0.0001
Vaxzevria	43.35	62.07	32.89	
Comirnaty	38.63	31.03	42.28	
Spikevax	14.59	3.45	21.48	
Ad26.Cov2.S	3.43	3.45	3.36	
Side effects after vaccination				< 0.0001
Yes	59.23	79.31	47.65	
No	40.77	20.69	52.35	

Data are expressed as percentage values. HM: herbal medicine.

Table 2
Sociodemographic characteristics of participants who received the second dose.

Item	Total (n = 181)	HM group (n = 47)	Non-HM group (n = 134)	P value
Gender				0.325
Male	67.40	71.88	64.71	
Female	32.60	28.13	35.29	
Age				< 0.0001
< 30 years	34.25	21.88	40.34	
30 s	29.28	43.75	21.01	
40 s	20.44	23.44	19.33	
50 s	12.15	10.94	13.45	
≥ 60 years	3.87	0.00	5.88	
Education level				< 0.0001
≤High school	13.81	1.56	20.17	
Bachelor's degree	53.04	53.13	52.94	
Master's degree	17.68	17.19	14.29	
Doctor's degree	15.47	28.13	12.61	
Region				0.592
Capital area	54.14	56.25	52.10	
Non-capital area	45.86	43.75	47.90	
Underlying disease				0.193
Yes	9.94	9.38	10.92	
No	90.06	90.63	89.08	
Vaccine brand				0.002
Vaxzevria	17.68	12.50	20.17	
Comirnaty	71.27	85.94	63.87	
Spikevax	11.05	1.56	15.97	
Side effects after vaccination				< 0.0001
Yes	48.62	73.44	35.29	
No	51.38	26.56	64.71	

Data are expressed as percentage values. HM: herbal medicine.

ond dose (68/88, 77.27%). The most severe side effect following both doses reported by participants was muscle pain and was experienced by 60 (43.47%) and 33 (37.50%) participants receiving the first and second doses, respectively (Table 3); 34 cases of mismatched vaccines did not report any side effect after the second dose.

In first dose, the median NRS score for side effects of Vaxzevria was higher than that of Comirnaty (P < 0.001), whereas the duration for the first dose of Vaxzevria was shorter than that of Comirnaty (P = 0.036). In second dose, the median NRS score for side effects of Spikevax was higher than that of Vaxzevria and Comirnaty (P = 0.010; Table 4).

Table 3
The most severe side effects of COVID-19 vaccines reported by participants.

Symptom	First dose (n = 138)					Second dose (n = 88)			
	Vaxzevria (n = 73)	Comirnaty (n = 39)	Spikevax (n = 21)	Ad26.Cov2.S (n = 5)	Total	Vaxzevria (n = 7)	Comirnaty (n = 68)	Spikevax (n = 13)	Total
Muscle pain	29	19	11	1	60	2	28	3	33
Fever	16	3	2	3	24	3	8	6	17
Headache	6	2	1	0	9	0	6	3	9
Nausea	3	2	1	0	6	0	2	0	2
Redness	0	3	0	0	3	0	2	0	2
Others	19	10	6	1	36	2	22	1	25

Table 4
Symptom-related variables of the side effects of COVID-19 vaccination.

Side effects	Vaxzevria	Comirnaty	Spikevax	Ad26.Cov2.S	P value	Post-hoc test (DSCF)
NRS score for the first dose	7 (5–8)	5 (3–7)	6 (4–7)	8 (7–8)	< 0.001	Vaxzevria > Comirnaty
NRS score for the second dose	5 (2–6)	6 (4–8)	8 (7–9)		0.010	Vaxzevria < Spikevax; Comirnaty < Spikevax
Onset for the first dose (days)	1 (0–1)	1 (0–1)	1 (1–2)	2 (1–3)	0.886	
Onset for the second dose (days)	1 (0–1)	1 (0.5–1)	1 (0–1)		0.895	
Duration for the first dose (days)	2 (1–3)	3 (2–5)	3 (2–4)	3 (2–4)	0.036	Vaxzevria < Comirnaty
Duration for the second dose (days)	1 (1–2)	3 (2–5)	3 (2–4)		0.800	

DSCF: Dwass, Steel, Critchlow-Filgner; NRS: numerical rating scale.

3.3. Use of HM

Among the 233 participants, 85 (36.5%) individuals reported that they took HM after their first vaccine dose, with no significant difference in use rates between men and women (Details of HM in Table 5). There were significant differences between the HM group and the non-HM group with respect to age and education levels (P < 0.0001) but no differences in region of residence or pre-existing conditions. Moreover, significant differences were observed between the HM group and the non-HM group with respect to vaccine brands and their side effects (P < 0.0001; Table 1). Among the 138 participants who experienced side effects after the first dose, the side effects were treated in 100. The results of the analysis, excluding 2 participants who could not provide precise dates, are shown in Table 6. The satisfaction level was significantly different between the HM and non-HM groups after the first dose (4.44 ± 0.87 *vs* 3.06 ± 1.06, respectively; P < 0.001), but NRS scores, the onset, and the duration of side effects were not significantly different (P = 0.604, 0.553 and 0.207, respectively; Table 6). After the first dose, the duration of HM use was 3.41 days on average. The NRS scores for side effects in the HM group were 6.55 ± 2.13 (before) and 3.12 ± 2.19 (after, P < 0.0001; Table 7). The NRS scores for side effects in the non-HM group were 6.27 ± 1.96 (before) and 3.48 ± 2.14 (after, P < 0.001).

Among the 181 participants, 47 (26.0%) reported that they took HM after the second dose of vaccine, with no significant difference between men and women. The HM and non-HM groups were significantly different with respect to age and education levels (P < 0.0001) but not in region of residence or pre-existing conditions. Again, significant differences were found between the HM group and the non-HM group with respect to vaccine brands and their side effects (P = 0.002; Table 2). Among the 88 participants who had side effects after the second dose, the side effects were treated in 50. The results of the analysis, excluding 3 participants who could not provide specific dates, are shown in Table 8. Significant differences between the HM and non-HM groups were also observed regarding the satisfaction level (4.57 ± 0.61 *vs* 3.47 ± 0.92, respectively; P < 0.001) and duration of side effects ([4.88 ± 5.44] d *vs* [2.53 ± 1.46] d, respectively; P = 0.029). However, the NRS scores and onset of side effects in the two groups were not significantly different (P = 0.727 and 0.446, respectively; Table 8). After the second dose, the average duration of HM use was 5.72 days. The NRS scores for side effects in the HM group were 6.78 ± 2.04 (before) and 2.69 ± 2.13 (after, P < 0.0001; Table 7).

Table 5
Details of herbal medicines.

Name of formula	Composition	g/pack
Shuanghetang	*Paeonia lactiflora* Pallas	10
	Rehmannia glutinosa Liboschitz ex Steudel	4
	Astragalus membranaceus Bunge	4
	Angelica gigas Nakai	4
	Cnidium officinale Makino	4
	Cinnamomum cassia Presl	3
	Glycyrrhiza uralensis Fischer	3
	Zingiber officinale Roscoe	4
	Zizyphus jujuba Miller var. inermis Rehder	6
Beidusan	*Panax ginseng* C. A. Meyer	4
	Bupleurum falcatum Linné	4
	Angelica decursiva Franchet et Savatier	4
	Ostericum koreanum Maximowicz	4
	Aralia continentalis Kitagawa	4
	Citrus aurantium Linné	4
	Platycodon grandiflorum A. De Candolle	4
	Cnidium officinale Makino	4
	Poria cocos wolf	4
	Glycyrrhiza uralensis Fischer	4
	Allium fistulosum Linné	3
	Mentha arvensis Linné var. piperascens Malinvaud ex Holmes	0.5
Shuangbaitang	Combination of Shuanghetang and Beidusan	
Gegentang	*Pueraria lobata* Ohwi	12
	Ephedra sinica Stapf	8
	Paeonia lactiflora Pallas	6
	Cinnamomum cassia Presl	4
	Glycyrrhiza uralensis Fischer	3
	Zingiber officinale Roscoe	4
	Zizyphus jujuba Miller var. inermis Rehder	6
Jiuweiqianghuotang	*Ostericum koreanum* Maximowicz	6
	Saposhnikovia divaricata Schischkin	6
	Cnidium officinale Makino	4
	Angelica dahurica Bentham et Hooker f	4
	Atractylodes lancea De Candlle	4
	Scutellaria baicalensis Georgi	4
	Rehmannia glutinosa (Gaertner) Liboschitz ex Steudel	4
	Asiasarum heterotropoides F. Maekawa var. mandshuricum F. Maekawa	2
	Glycyrrhiza uralensis Fischer	2

Table 6
Variables among participants who treated side effects with HM after the first dose.

Variable	HM group (n = 66)	Non-HM group (n = 32)	P value
Satisfaction	4.44 ± 0.87	3.06 ± 1.06	< 0.001
NRS score of side effects after the vaccination	6.55 ± 2.13	6.31 ± 1.97	0.604
Onset of side effects after the vaccination (days)	1.03 ± 1.25	1.31 ± 2.53	0.553
Duration of side effects after the vaccination (days)	3.89 ± 5.75	2.94 ± 1.44	0.207

HM: herbal medicine; NRS: numerical rating scale.

Table 7
Comparison of vaccine side effects among participants who took HM.

Side effects after the vaccination	Before HM	After HM	P value
NRS score for the first dose (n = 66)	6.55 ± 2.13	3.12 ± 2.19	< 0.0001
NRS score for the second dose (n = 32)	6.78 ± 2.04	2.69 ± 2.13	< 0.0001

HM: herbal medicine; NRS: numerical rating scale.

Table 8
Variables among participants who treated side effects with HM after the second dose.

Variable	HM group (n = 32)	Non-HM group (n = 15)	P value
Satisfaction	4.57 ± 0.61	3.47 ± 0.92	< 0.001
NRS score of side effects after the vaccination	6.78 ± 2.04	6.47 ± 2.26	0.727
Onset of side effects after the vaccination (days)	1.34 ± 2.54	0.93 ± 1.22	0.446
Duration of side effects after the vaccination (days)	4.88 ± 5.44	2.53 ± 1.46	0.029

HM: herbal medicine; NRS: numerical rating scale.

The NRS scores for side effects in the non-HM group were 6.30 ± 2.22 (before) and 3.26 ± 2.18 (after, P < 0.001).

The most frequently used herbal formula after the first dose was based on Shuanghetang (21/66, 31.82%; Fig. 1). The most common HM for prophylaxis in cases without side effects was also based on Shuanghetang (6/18, 33.33%). Over half of the participants in the HM group (43/66, 65.15%) started taking HM on the day of vaccination. The number of participants receiving a dose of HM before vaccination (10/66, 15.15%) was similar to that of participants receiving a dose of HM after vaccination (13/66, 19.70%). The duration of HM use was 3 days (26/66, 39.39%), 2 days (16/66, 24.24%) or 1 day (9/66, 13.64%). There was one report of fatigue as a side effect in the HM group.

After the second dose, Jiuweiqianghuotang was the most frequently used HM (11/32, 34.38%; Fig. 1), whereas Shuanghetang was the most common herbal formula used for prophylaxis without any side effects (3/11, 27.27%). Half of the participants in the HM group (16/32, 50.00%) started taking HM on the day of vaccination. The number of participants receiving a dose of HM before vaccination (3/32, 9.38%) was lower than that of participants receiving a dose of HM after vaccination (10/32, 31.25%). The duration of HM use was 2 days (8/32, 25.00%), 3 days (8/32, 25.00%) or 5 days (6/32, 18.75%). Leg edema was reported as a side effect by one participant of the HM group.

4. Discussion

This study explored the use of HM to counter the side effects of COVID-19 vaccines. In previous studies, 75.8% of participants had side effects, such as pain and tenderness [18], and 94.2% of people who received Spikevax had pain at the injection site [19]. Riad et al. [20] found that 89.8% of vaccinated people had muscle pain. Riad et al. [21] also reported that 91.6% of people who had received an mRNA-based vaccine had at least one side effect. This was also

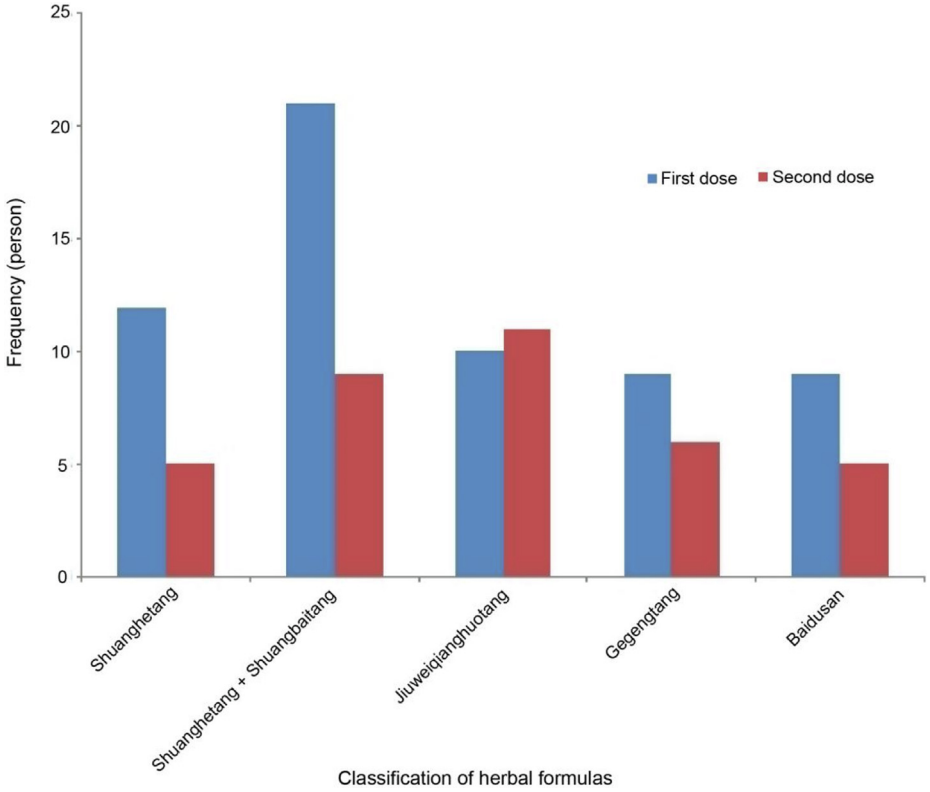

Fig. 1. Frequency of herbal formulas used to counter the side effects of COVID-19 vaccination.

the case with other studies that found more side effects in women and younger age groups. Klugar et al. [22] reported that mRNA-based COVID-19 vaccines were associated with local side effects and that viral vector-based vaccines were associated with systemic side effects. Moreover, women and younger groups were concerned about the side effects.

In the current study, 59.23% (138/233) of participants reported side effects following their first dose and 48.62% (88/181) following their second dose. These results were higher than that of the study of Polack et al. [23]. Many factors can lead to side effects; therefore, determining the main cause was difficult. However, the mixing of vaccine suppliers between first and second doses could not be ruled out. Some studies [24–26] have reported the safety and efficacy of the mix and match of COVID-19 vaccines. Based on these data, many countries proceeded with the vaccination using several kinds of vaccines. Since the COVID-19 marks the first mass application of mRNA vaccines, long-term monitoring should be conducted. Despite the administration of a booster or additional vaccination for preventing hospitalization and reducing severity, criticality and fatality of COVID-19 vaccines [27], the level of antibodies naturally drops after a vaccination. To maintain a constant high-level of antibodies for everyone is impossible. Nonetheless, for herd immunity and reduction of severity, criticality and fatality in vulnerable groups, additional doses of vaccine must be administered over time.

The majority of individuals in the HM group that experienced side effects from the COVID-19 vaccines were in their thirties with a bachelor's degree, whose first dose was Vaxzevria and second dose was Comirnaty. It was sociologically similar to other studies [28–31], in that typical participants were middle-aged and well-educated, except gender in the HM group.

The participants of HM group who reported side effects after vaccination were about twice compared with those of non-HM group. The satisfaction level for HM was higher for both first and second doses, and the duration of side effects for the second dose was longer in the HM group than in the non-HM group. This might imply there was preference based on the relation that participants in the HM group suffered from side effects of vaccines more and longer therefore got prescription of HM to relieve the symptoms. It could affect satisfaction, but more research is needed, such as revealing whether it was due to lack of guidelines to alleviate side effects of vaccination.

The most administered type of vaccine and the most frequently prescribed HM were different between the first and second doses. According to the United States Centers for Disease Control and Prevention, the prevalence of pain, edema, and redness was lower in individuals who received Comirnaty than in those who received Spikevax [32,33]. We obtained the same result in this study. However, the duration for the first dose, NRS scores, and onset of the side effects for both doses were not significantly different, but the duration for the second dose of them was different. For both first and second doses of COVID-19 vaccines, the use of HM resulted in significant improvements in side effect symptoms. In surveys of HM use in Republic of Korea, the prevalence of those who have used HM at least once was 74.4% in 1991 [34], 70% in 2000 [35], 93.8% in 2007 [36], and 85.5% in 2014 [37]. However, few studies investigated the associations between COVID-19 vaccinations and medication use; one study examined the use of antiepileptics [38] and another examined antihistamines [39]. Some previous studies have shown that HMs have anti-SARS-CoV effects, such as *Isatis tinctoria L.* [40], *Lycoris radiata* (L'Hér.) Herb., *Artemisia annua* L., *Pyrrosia lingua* (Thunb.) Farw. [41], *Bupleurum falcatum* L., *Heteromorpha trifoliata* (H.L.Wendl.) Eckl. & Zeyh., *Scrophularia scorodonia* L [42] and *Torreya nucifera* (L.) Siebold & Zucc [43]. However, these studies were limited to non-human research. No prior studies tested the use of HM with vaccines except for the use of Shiquandabutang and Buzhongyiqitang with a vaccine for human papillomavirus in mice [44]. Recently, one study reported the relationship between side effects of COVID-19 vaccines and HM [45]. It did not use numeric scales and reported a range of treatments, including HM; thus, understanding the specific role played by HM was difficult. However, it provided good evidence for the status of HM use at that time (April 2021). The survey period of that study (directly after initial vaccination with Vaxzevria, mainly) was different from this study (around the administration of the second dose of mRNA vaccines).

The most frequent herbal formula used in the current survey was based on Shuanghetang. Shuanghetang combined with Xiaojianzhongtang and Siwutang is used to improve fatigue, liver function and inflammation and to relax smooth muscles [46,47]; therefore, it is prescribed to patients who are exhausted due to illness. In addition, it helps to activate antigen-specific immune responses [48]. After the second dose of vaccine, Jiuweiqianghuotang was the most used. The formula of Jiuweiqianghuotang is different from Shuanghetang; however, it has anti-inflammatory and analgesic activity [49], and it is also used to treat common cold, headache, arthritis and fever. Safety is guaranteed along with efficacy [50,51]. Kang et al. [45] also reported that patients were using HMs—Jiuweiqianghuotang (15/38, 16.77%), Gegentang (9/38, 10%) and Shuanghetang (5/38, 5.56%)— to treat side effects of the COVID-19 vaccines. Although the ratios of HM use were dissimilar, there was good overlap in HM selection between our study and the study of Kang et al. Further, HMs recommended for prophylaxis by KM doctors were Qiongyugao, Gongchendan and Jiuweiqianghuotang, and these are different from the HMs included in this study. Qiongyugao and Gongchendan are generally used for strengthening during weakness [52] and enhancing the immune system [53]. They are plausible recommendations in theory, but different in real world from this study, indicating that Shuanghetang was prescribed not only for recuperation, but also for treatment; more than half of participants took HM from the day they got vaccinated. The clinical use of Shuanghetang is practical, not theoretical, and should be included in the official HM guidelines.

For participants in this study, the duration of HM use was typically less than one week. It could not be ruled out that the prescription period might have been determined according to the duration of symptoms, but other factors might have affected it. In general, the HM prescriptions from KM doctors are intended to be taken for around 2 weeks as boiled type or a few days as soft extract, tablet or powder type. In Republic of Korea, doses of Jiuweiqianghuotang, Baidusan and Gegentang covered under NHI are manufactured as soft extract, tablet or powder type; therefore, the prescribing and the taking of HM are easier and the cost for HM is lower. Thus, the available formulations of the medications may have affected the average duration of HM use. However, Shuanghetang was not covered under NHI and was the most frequently prescribed formula, suggesting the presence of factors other than the type and cost of HM. Consequently, the MOH should consider covering more types of HM through NHI or expanding the pilot projects investigating HM efficacy.

Nonetheless, this survey only included participants taking HM by prescription, which is common in Republic of Korea because some HMs were covered under NHI. However, the NHI did not support all uses of HM such as use without medical supervision, which is more dangerous, particularly for children, the elderly and pregnant women [54,55]. Therefore, the guidelines for HM use to reduce side effects of COVID-19 vaccines must be established by conducting more research.

In addition, there are some limitations in this study. First, this was an online survey conducted in Republic of Korea. The sample group may not represent the general population because of limited access to information, which would have affected the study results.

Therefore, it is difficult to generalize the findings to other countries and vaccines. Second, the relationship between outcome and exposure could not be determined because it was a cross-sectional study. Third, recall and selection bias occurred by self-reporting and enrolling participants collected by APKOM members. Fourth, vaccination policies are still changing. In Republic of Korea, when vaccines first became available, most people were vaccinated with Vaxzevria. Later, vaccines of other brands emerged and received approval; the most frequently used vaccines are now Comirnaty and Spikevax. Thus, some people have received more than two brands of vaccines, and this may have affected the results. However, the study design did not consider this factor. Fifth, side effects generally occur within a few days of vaccination; however, as some participants answered the survey just after vaccination, they may not have experienced any side effects until after the survey. Generalization to other populations is difficult because of these limitations.

5. Conclusions

Side effects had higher NRS scores and shorter durations in participants whose first dose of vaccine was Vaxzevria compared to Comirnaty. At the second dose, NRS scores for side effects were higher for Spikevax than for Vaxzevria and Comirnaty. Approximately a third of participants used HM to alleviate the side effects of COVID-19 vaccines. HM use was associated with age, education level, vaccine brand, and whether participants experienced side effects after vaccination or not. HM use was also associated with a higher satisfaction. The most frequently used herbal formula was based on Shuanghetang. Further studies are needed to gather data on the use of HM to counter the side effects of vaccines and to confirm these findings.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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