Research Article

Do Herbal Formulas Influence the International Normalized Ratio of Patients Taking Warfarin? A Retrospective Study

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Warfarin is a common anticoagulant agent for cardiovascular diseases, and it is known to interact with several foods and drugs. Several studies report an interaction between warfarin and herbal medicines; however, the influence of herbal medicines on the international normalized ratio (INR) is still controversial. We investigated the influence of herbal formulas on INR of patients taking warfarin. We searched electronic medical records of inpatients for INR results. Then, we compared the changes in INR and any adverse events between the group taking herbal formulas and warfarin (herbal group) and another group taking warfarin only (nonherbal group). Eighty-six patients were included; 45 patients were assigned to the herbal group and 41 patients to the nonherbal group. The herbal group had taken the same dose of warfarin for a longer period. The nonherbal group had a slightly higher mean INR value than the herbal group. The ratio of INR less than 2 and greater than 3, the ratio of INR that increased or decreased by one or more compared to the initial INR, and the ratio of adverse events were not significantly different between the two groups. It is suggested that use of herbal formulas may not influence INR value.

1. Introduction

Warfarin is a common anticoagulant agent that is used in various cardiovascular diseases, venous thrombosis, prevention of systemic embolism, atrial fibrillation, and cardiac valve diseases [1]. It is known to interact with several drugs and foods to influence the international normalized ratio (INR) [2]. Herbal formulas have been used for several thousands of years in China, Korea, and Japan; in recent years, many Western countries have started using herbal formulas [3]. As many countries use herbal formulas, the potential effects of these herbal formulas on the INR have been reported [4–6]. In one report, an herbal formula combination of Tribulus terrestris, Avena sativa, and Panax ginseng was reported to result in a sudden increase in the INR of patients who took warfarin for aortic valve replacement or atrial fibrillation [4]. However, another randomized controlled trial study reported that Panax ginseng did not have any effect on INR [7]. Whether or not herbal formulas influence INR is still controversial.

Several previous researchers have reported interactions between herbal formulas and warfarin, but there are few citations published in Science Citation Index (SCI) journals, and there are some important limitations in all of the studies [8–15]. Choi et al. investigated the interaction between herbal formulas and warfarin in 27 patients using the World Health Organization-The Uppsala Monitoring Centre causality categories and modified drug interaction probability scale (mDIP scale). However, the study could not clearly clarify interactions between herbal formulas and warfarin because the mDIP scale only measures single components and is not suitable for complex formulas. Kim et al. [9], Lee et al. [10], Kim et al. [11], and Lee and Ryu [12] investigated patients taking warfarin who were hospitalized at a traditional Korean Medicine hospital. Kim et al. [9] reported that herbal formulas may slightly affect INR, but other studies reported that herbal formulas did not affect INR [10–12]. Kwon et al. [13] and Jung et al. [14] investigated the mean INR of patients taking warfarin and found no statistically significant differences between INR before and INR during the use of the
herbal formulas. The results by Jung et al. [14] are limited because they only investigated the mean INR; the data does not show the change in INR in the individual subjects as a result of the herbal formulas. In another study, Kwon et al. [15] investigated 28 patients who took Panax ginseng in conjunction with warfarin. Because the study only investigated herbal formulas that included Panax ginseng, it was difficult to apply the findings to other herbal formulas that do not contain Panax ginseng.

In this study, we compared a group taking herbal formulas in conjunction with warfarin (herbal group) and another group taking warfarin only (nonherbal group) in order to investigate whether herbal formulas affect INR.

2. Materials and Methods

The study was performed in accordance with the ethical standards of the Helsinki Declaration. The Institutional Review Board of Kyung Hee University Hospital at Gangdong approved this study (KHNMC-OH-IRB2013–015).

We searched electronic medical records of patients hospitalized from June 2006 to May 2013 at the Department of Korean Medicine or the Department of Physical Medicine and Rehabilitation in Stroke and Neurological Disorders Center, Kyung Hee University Hospital, at Gangdong to find patients who satisfied our criteria: (1) 18 years of age or older, (2) previously taking warfarin before hospitalization and taking the same dose of warfarin for at least five days since the day of hospitalization, (3) initial INR in the range of 2 to 3, and (4) follow-up measurements conducted once or more during hospitalization. In order to exclude the possible effects on INR, any patients that had taken any herbal medicine in the 30 days before hospitalization were excluded. If the patients were hospitalized more than twice, we regarded each hospitalization as an individual subject. In addition, we designated patients who took herbal formulas with warfarin as the herbal group and those who took only warfarin as the nonherbal group. We then investigated the following items for up to 30 days: (1) ratio of INR less than two and greater than three, (2) ratio of INR changed by one or more from the initial INR, (3) mean INR, and (4) ratio and types of adverse events. If warfarin dose was changed, a patient was discharged in either group, or in a patient in the nonherbal group started taking an herbal formula, we investigated INR and adverse events up to the time of that change.

Herbal formulas were prescribed decoctions or extracts. Herbal medicines for decoctions were purchased from Kyung Hee Herb Pharm Co. (Seoul, Korea), and extracts were purchased from the following companies: Kyung Hee Herb Pharm Co. (Seoul, Korea), Tsumura Co., Ltd. (Tokyo, Japan), Hamsoa Pharmaceutical Co., Ltd. (Seoul, Korea), Kwang Dong Pharmaceutical Co., Ltd. (Seoul, Korea), Jeil Hanbang Co., Ltd. (Seoul, Korea), Hankook Shinyak Pharm Co., Ltd. (Chungcheongnam-do, Korea), and Kiwha Bio Co., Ltd. (Gyeongsangnam-do, Korea). Decoctions were prepared using two or more herbal ingredients in 1.2 to 1.5 liters of water boiled in decoction vessels at greater than 100°C for 2 hrs 30 min. All patients in the herbal group took herbal decoctions of 50 mL to 120 mL, 2 hrs after every meal, and took extracts of 6–18 g according to symptoms, if needed.

2.1. Statistical Analyses. Data are expressed as number or mean ± standard deviation. Categorical variables were analyzed by Pearson's Chi-square test, and continuous variables were analyzed by Student's t-test. P values less than 0.05 were considered significant. All data were analyzed using SPSS for Windows, version 18.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA).

3. Results

Eighty-six patients were included; 45 patients were assigned to the herbal group and 41 patients were assigned to the nonherbal group. The herbal group took the same dose of warfarin for a longer period (P = 0.027), had more cerebral infarction as an indicator of warfarin use (P = 0.036), and showed a higher hemoglobin count (P = 0.045) compared to the nonherbal group. There were no statistically significant differences in other baseline characteristics between the two groups (Table 1).

There were no statistically significant differences in the ratio of INR less than 2 or greater than 3 or the ratio of increase/decrease of more than one from the initial INR between the two groups. However, the nonherbal group had a slightly higher mean INR value than the herbal group (Table 2).

No major bleeding was reported in any patients, but there were some minor bleeding events in both groups. In the herbal group, one patient appeared to have hemoptysis during tracheostomy suctioning, one showed hematuria, and another patient showed melena. In the nonherbal group, one patient complained of hematuria, and another patient showed hemoptysis and subconjunctival hemorrhage. None of these adverse events were fatal, and all patients showed recovery. There was no statistically significant difference in the adverse events ratio between the two groups (Table 3).

4. Discussion

Warfarin is an antagonist of vitamin K and is known to interact with several foods and drugs [2]. Because of its narrowing therapeutic index, patients require consistent monitoring when taking warfarin [16]. Several studies have reported that herbal formulas affect INR; however, there were limits to the research methods used in these studies, so the issue is still controversial [7–15]. In this study, we found no substantial differences between the herbal and the nonherbal groups with regard to the ratio of INR less than two and greater than three or the ratio of INR value changed by one or more units from the initial INR. Some previous studies reported that herbal medicines could affect INR [17, 18]; in these cases, the herbal medicines were administered by the patients themselves and were not prescribed by experts. In contrast, some randomized controlled trials reported that herbal formulas prescribed by experts did not affect INR [10–14]. Similar results were shown in our study; therefore, we concluded that even if some patients took herbal formulas that contain Panax ginseng, Dong quai, and other medicines that can affect INR [19], the influence may be prevented when the herbal formulas
### Table 1: Baseline characteristics between the herbal and nonherbal groups.

|                         | Herbal group (n = 45) | Nonherbal group (n = 41) | P value |
|-------------------------|-----------------------|--------------------------|---------|
| Male/female             | 19/26                 | 17/24                    | 0.943   |
| Age (year)              | 70.0 ± 12.0           | 70.5 ± 12.8              | 0.842   |
| Admission days          | 26.5 ± 5.7            | 23.9 ± 7.6               | 0.077   |
| Period of taking the same dose of warfarin (days) | 15.6 ± 8.0 | 11.9 ± 7.6 | 0.027* |
| Reason for hospitalization |                       |                          | 0.274   |
| Cerebral infarction     | 43                    | 38                       |         |
| Intracerebral hemorrhage| 0                     | 2                        |         |
| Epidural hemorrhage     | 0                     | 1                        |         |
| Subarachnoid hemorrhage | 1                     | 0                        |         |
| Parkinson's disease     | 1                     | 0                        |         |
| Medical history         |                       |                          |         |
| Hypertension            | 37                    | 29                       | 0.208   |
| Diabetes mellitus       | 17                    | 9                        | 0.110   |
| Dyslipidemia            | 13                    | 16                       | 0.321   |
| Cerebral infarction     | 10                    | 4                        | 0.118   |
| Indicators of warfarin  |                       |                          |         |
| Cerebral infarction     | 9                     | 2                        | 0.036*  |
| Valvular heart disease (non-op) | 1                | 1                        | 0.947   |
| Valvular heart disease (op) | 0                   | 3                        | 0.065   |
| Coronary artery disease | 0                     | 2                        | 0.134   |
| Atrial fibrillation     | 35                    | 31                       | 0.812   |
| Pulmonary embolism      | 1                     | 2                        | 0.503   |
| Patent foramen ovale    | 1                     | 0                        | 0.337   |
| Aortic dissection       | 0                     | 1                        | 0.292   |
| Medications             |                       |                          |         |
| Antiplatelet drugs      | 7                     | 10                       | 0.304   |
| Antihypertensive drugs  | 32                    | 25                       | 0.321   |
| Antidiabetic drugs      | 13                    | 6                        | 0.112   |
| Antidyslipidemic drugs  | 14                    | 17                       | 0.318   |
| Warfarin dose (mg/day)  | 3.0 ± 1.4             | 3.3 ± 1.5                | 0.258   |
| Initial INR (INR)       | 2.4 ± 0.3             | 2.4 ± 0.3                | 0.371   |
| Number of tests of INR  | 4.6 ± 2.5             | 4.7 ± 2.8                | 0.981   |
| Initial laboratory findings |                        |                          |         |
| AST (IU/L)              | 23.8 ± 9.8            | 23.8 ± 10.3              | 0.992   |
| ALT (IU/L)              | 22.8 ± 16.3           | 24.1 ± 18.9              | 0.719   |
| BUN (mg/dL)             | 16.5 ± 6.3            | 17.6 ± 6.1               | 0.470   |
| Creatinine (mg/dL)      | 0.89 ± 0.27           | 0.86 ± 0.25              | 0.561   |
| Platelet (×10^3/μL)     | 265.9 ± 96.3          | 254.6 ± 81.2             | 0.559   |
| Hemoglobin (g/dL)       | 13.85 ± 5.23          | 12.12 ± 1.61             | 0.045*  |
| Hematocrit (%)          | 42.40 ± 31.94         | 35.78 ± 4.39             | 0.192   |

*non-op: without operation history, op: with operation history, INR: international normalized ratio, BUN: blood urea nitrogen, AST: aminotransferase, and ALT: alanine transferase.

Student’s t-test was used for continuous variables, and Pearson’s Chi-square test was used for categorical variables. Data are expressed as number or mean ± standard deviation; *P < 0.05 was considered significant.

### Table 2: Changes in the international normalized ratio between the herbal and nonherbal groups.

|                         | Herbal group (n = 45) | Nonherbal group (n = 41) | P value |
|-------------------------|-----------------------|--------------------------|---------|
| INR greater than 3 (%)  | 9 (20.0)              | 16 (39.0)                | 0.052   |
| INR less than 2 (%)     | 27 (60.0)             | 17 (41.5)                | 0.086   |
| INR changed by one or more units (%) | 12 (26.7)          | 11 (28.8)                | 0.986   |
| INR increased by one or more units (%) | 7 (15.6)            | 6 (14.6)                 | 0.905   |
| INR decreased by one or more units (%) | 5 (11.1)             | 6 (14.6)                 | 0.625   |
| Mean INR (mean ± SD)    | 2.3 ± 0.4             | 2.4 ± 0.4                | 0.032*  |

INR: international normalized ratio.

Data are expressed as number or mean ± standard deviation; *P < 0.05 was considered significant. Statistical analysis by Pearson’s Chi-square test.
Table 3: Adverse events ratio between the herbal and nonherbal groups.

| Herbal group (n = 43) | Nonherbal group (n = 41) | P value |
|----------------------|--------------------------|---------|
| Patient number (%)   |                          |         |
| 3 (6.7)              | 2 (4.9)                  | 0.723   |

Data are expressed as number or mean ± standard deviation; P < 0.05 was considered significant. Statistical analysis by Pearson's Chi-square test.

Table 4: Frequency of use of herbal medicines taken by patients with an INR less than 2.

| Herbal medicines                                      | Frequency (%) |
|-------------------------------------------------------|---------------|
| Glycyrrhiza uralensis Fisch., Poria cocos (Schw.) Wolf | 27 (2.1)      |
| Angelica gigas Nakai, Dioscorea batatas Decne., Scutellaria baicalens Georgi | 26 (1.1)      |
| Cinnamomum loureiri Nees, Zizyphus jujuba var. inermis Rehder, Ledebouriella divaricata (Turcz.) Hiroe, Panax ginseng C. A. Mey. | 24 (1.8)      |
| Liriopis platyphylla Wang et Tang, Paeonia obovata Maxim., Atractylodes japonica Koidz. | 23 (1.7)      |
| Plantago asiatica L., Zingiber officinale Rosc., Cnidium officinale Makino | 22 (1.7)      |
| Bupleurum falcatum Linne | 21 (1.6)      |
| Rhamnus sativus L., Apis indica Radoszkowski, Citrus unshiu Markovich | 20 (1.5)      |
| Triticum aestivum L. | 19 (1.4)      |
| Dryobalanops camphora Colebr., Prunus sibirica L., Rehmannia glutinosa (Gaertner) Libosch. | 18 (1.4)      |
| Aurum, Moschus moschiferus L. | 17 (1.3)      |
| Angelica koreanum (Max.) Kitagawa, Pinellia ternata (Thunb.) Breit. | 16 (1.2)      |
| Glycine max Merr., Ampelopsis japonica (Mak.) Makino, Zizyphus jujuba Mill, Equus asinus L., Gazella subgutturosa Guld., Schizandra chinensis (Turcz.) Baill., Bos taurus domesticus Gmelin, Typha orientalis Presl | 15 (1.1)      |
| Polypogon tenuifolium Willd. | 14 (1.1)      |
| Acorus gramineus Sol. ex Aiton, Dimocarpus longan Lour., Gardenia jasminoides J. Ellis | 13 (1.0)      |
| Angelica dahurica Benth. et Hooker I., Amomum volsum Lour., Alisma canaliculatum All. Br. et Bouche | 12 (0.9)      |
| Rheum palmatum var. palmatum, Hordeum vulgare var. hexastichon Aschers., Inula helenium L., Cimicifuga japonica Spreng., Atractylodes japonica Koidz., Cyperus rotundus L. | 11 (0.8)      |
| Pueraria thunbergiana Benth., Chrysanthemum indicum L., Citrus aurantium L., Poncirus trifoliata Rafin., Atragalus membranaceus Bunge, Cotis chinensis Franch | 10 (0.8)      |
| Heracleum hemsleyanum Michx., Ephedra sinica Stapf., Crataegus pinnatifida Bge., Cornus officinalis Sieb. et Zucc., Coix lacryma-jobi L., Phellodendron amurense Rupr., Magnolia officinalis Rehder et Wilson, Forsythia koreana Nakai | 9 (0.7)      |
| Paeonia suffruticosa Andrews, Polygonum multiflorum Thunb., Phyllostachys nigra var. henonis (Bean.) Stapf, Schizonepeta tenuifolia (Benth.) Briq. | 8 (0.6)      |
| Castanea crenata S. et Z., Thuja orientalis L., Plantago alata Nakai, Asparagus cochinchenhins Merr., Aconitum carmichaeli Debx, Arecaceae L. | 7 (0.5)      |
| Trichosanthes kirilowii Maxim., Arisaema amurense Maximowicz, Cannabis sativa L., Asarum sieboldii var. seoulense Nakai, Perilla frutescens var. acuta Kudo, Achyranthes bidentata Bl., Anthriscus sylvestris var. hirtifuctus Harra, Carthamus tinctorius L., Lonicera japonica Thunb. | 6 (0.5)      |
| Angelica tenuissima Nakai, Pogostemon cablin (Blanco) Benth., Mentha arvensis var. piperascens MalinV, Nelumbo nucifera Gaertner Polyponds umbellatus (Pers.) Fries | 5 (0.4)      |
| Juncus effusus var. decipiens Buchen., Chaenomeles sinensis Koehne, Akebia quinata var. polyphylla Nak., Morus alba L., gypsy, Clematis brachyura Max. | 4 (0.3)      |
| Salvia miltiorrhiza Bunge., Sinomenium acutum Rehder et Wils., Amomum cardamomum L., Curcuma zedoaria Rosc., Scirpus fluviatilis (Torr.) A. Gray, Panax notoginseng (Burk.) F. H. Chen, Dendrobium moniliforme (L.) Sw, Lamiun album L., Alpinia oxyphylla Miq., Buthus martensiicarsch., Anemarrhena asphodeloides Bunge, Citrus reticulata Blanco, Talc | 3 (0.2)      |
| Terminalia chebula var. tomentella Kirt., Oryza sativa L., Dianthus chinensis L., Cibotium barometz J. Smith, Capreolus capreolus ochracea Thomas, Eucommia ulmoides Oliv., Vitex trifolia L., Sinapis alba L., Liquidambar orientalis Mill., Styrox benzoin Dryand., Acanthopanax seoulense Nakai, Rhinoceros unicornis L., Linderia strychnifolia (Sieb. et Zucc.), Pistacia lentiscus Joel, Paonia obovata Max., Eugenia carphorylata Thunb., Aguilaria agallocha Roxb., Psoralea corylifolia L., Croton tiglium L., Fritillaria verticillata var. thunbergii (Miq.) Baker, Polygonum bellardi var. effusum Meisn, Piper longum L., Schoehalia buergeriana Miq. | 2 (0.2)      |
| Alpinia officinarum Hance, Prunus persica (L.) Batsch, mirabilite, Bombyx mori L., Dolichos lablab L., Rubus schizostylus Lev., Adenophora triphylla var. hirsuta Nakai, Morus alba L., Perilla sikkokiana Nakai, Gentiana jamesii Hemsl., Arctium lappa L., Prunus shidoyanaka Nakai, Artemisia scoparia Waldst. et Kit., Polygonum multiflorum Thunb., Uncaria sinensis (Oliv.) Havli., Lycium barbarum L., Sanguisorba longifolia Bertol., Gentiana macrophylla Pall., Trichosanthes kirilowii Maxim., Cascus chinensis Lam., Taraxacum sinicum Kitag | 1 (0.1)      |
were prescribed by experts after medical examination. We described the herbal medicines that had been taken by members of the herbal group in Tables 4–6. There were three patients in the herbal group and two patients in the nonherbal group that showed adverse events. In the herbal group, one patient showed an INR lower than the therapeutic range, a second showed an INR within the therapeutic range, and the third showed an INR higher than the therapeutic range. All patients had bleeding risk factors that were directly associated with adverse events for inpatient taking warfarin, so we considered that the clinical situations were fully reflected and all medicines that had been taken were identified. To our knowledge, this is the first retrospective study of a comparison between a warfarin-treated group and a group who took warfarin in conjunction with herbal formulas. We investigated not only mean INR, but also changes in INR and adverse events; therefore, the data will be useful to clinicians and for further studies.

Because our study period was short, we cannot show the long-term effects of herbal formulas on INR, and the data do not represent the influence of herbal formulas on INR that were not within the therapeutic range or the effects of individual herbal medicines. In the future, large-scale, long-term, prospective, and individual herbal medicines studies will be needed.

5. Conclusion

In this study, the ratio of INR less than 2 and greater than 3, the ratio of INR that increased or decreased by one or more
Table 6: Frequency of use of herbal medicines taken by the herbal group.

| Herbal medicine                                                                 | Frequency (%) |
|---------------------------------------------------------------------------------|--------------|
| Glycyrrhiza glabra L.                                                            | 45 (2.0)     |
| Angelica acutiloba Kitag., Dioscorea tenuipes Fr. et Sav., Scutellaria baicalensis Georgi | 49 (1.9)     |
| Thuja orientalis L., Paonia lactiflora Pallas, Poria cocos (Schwe.) Wolf         | 41 (1.8)     |
| Lithop platyphylla Wang et Tang, Atractylodes macrocephala Koidz, Ligusticum wallichii var. officinale Yook, Zingiber officinale | 40 (1.8)     |
| Platycodon grandiflorum (Jacq.) A. DC., Zizyphus jujuba var. inermis Rehder, Ledebouriella divaricata (Turcz.) Hironoe, Cinnamomum cassia Blume | 39 (1.7)     |
| Panax ginseng C. A. Mey.                                                         | 38 (1.7)     |
| Bupleurum falcatum Linne                                                         | 36 (1.6)     |
| Triticum aestivum L.                                                             | 35 (1.5)     |
| Apis indica Radoszkowski                                                        | 34 (1.5)     |
| Dryobalanops camphora Colebr.                                                    | 33 (1.5)     |
| Raphanus sativus L., Prunus sibirica L.                                         | 32 (1.4)     |
| Aurum, Moschus moschiferus L., Rehmannia glutinosa (Gaertner) Libosch.           | 31 (1.4)     |
| Citrus unshiu Markovich                                                         | 29 (1.3)     |
| Glycine max Merr., Pinellia pedatisecta Schott, Ampelopsis japonica (Mak.) Makino, Equus asinus L., Gazella subgutturosa Guld., Bos taurus domesticus Gmelin, Typha orientalis Presl | 28 (1.1)     |
| Zizyphus jujuba Mill, Schizandra chinensis (Turcz.) Baill., Polygala sibirica L. | 25 (1.1)     |
| Notopterygium forbesii Boiss, Rheum palmatum L., Dimocarpus longan Lour., Gardenia jasminoides var. grandiflora (Lour.) Nakai | 23 (1.0)     |
| Acorus gramineus Sol. ex Aiton, Captis chinensis Franch                         | 21 (0.9)     |
| Hordeum vulgare L., Inula helenium L., Anomum villosum Lour., Astragalus membranaceus Bunge | 20 (0.9)     |
| Chrysanthemum indicum L., Alisma orientalis (Sam.) Juzep., Cyperus rotundus L., Phellodendron amurense Rupr. | 19 (0.8)     |
| Pueraria thunbergiana Benth., Cimicifuga heracleifolia Kom.                    | 18 (0.8)     |
| Atractylodes lancea (Thunb.) DC.                                                | 17 (0.7)     |
| Angelica pubescens for. biserrata Shan et Yuan, Crataegus pinnatifida Bge, Citrus aurantium L., Magnolia officinalis Rehder et Wilson | 15 (0.7)     |
| Ephedra sinica Stapf., Cornus officinalis Sieb. et Zucc., Lonicera japonica Thunb. | 14 (0.6)     |
| Paonia suffruticosa Andrews, Phyllostachys nigra var. henonis (Bean.) Stapf, Poncirus trifoliata Rafin., Plantago alata Nakai, Schizonepeta tenuifolia (Benth.) Briq. | 13 (0.6)     |
| Angelica tenuissima Nakai, Asarum sieboldii Miq., Coix lacryma-jobi L., Asparagus cochinchinensis Merr. | 12 (0.5)     |
| Aconitum koreanum R. Raymond, Polygonum multiflorum Thunb., Nelumbo nucifera Gaertner | 11 (0.5)     |
| Mentha arvensis var. pipercascens Maliniv                                             | 10 (0.4)     |
| Agastache rugosa (Fisch. et Meyer) O. Kuntze, Trichosanthes kirilowii Maxim., Arisaema erubescens (Wall). Schott, Juncus effusus var. decipiens Buchen., gypsum, Forsythia suspensa (Thunb.) Vahl, Achyranthes bidentata BL., Peucedanum decursivum (Miq.) Maxim., Areca catechu L. | 9 (0.4)      |
| Castanea crenata S. et Z., Akebia quinata DeCne., Perilla frutescens var. acuta Kudo | 8 (0.4)      |
| Cannabis sativa L., Chaenomeles sinensis Koehne, Aconitum carmichaeli Debx, Clematis mandshurica Rupr., Polyposor umbellatus (Pers.) Fries, Anemarrhena asphodeloides Bunge, Carthamus tinctorius L., Talc | 7 (0.3)      |
| Dianthus chinensis L., Polygonon aviculare Linne                                    | 6 (0.3)      |
| Vitex rotundifolia L. Fil., Amomum kravanth Pierre ex Gagnep, Curcuma zedoaria Rosc., Scirpus fluvialtilis (Torr.) A. Gray, Morus alba L., Dipsacus asper Wall, Alpinia oxyphylla Miq., Citrus unshiu Markovich | 5 (0.2)      |
| Terminalia chebula var. tomentella Kurt., Salvia miltiorrhiza Bunge., Eucommia ulmoides Oliv., Sinomenium acutum Rehder et Wils., Panax notoginseng (Burk.) F. H. Chen, Dentrobiurn loddigesii Rolfe., Liquidambar orientalis Mill., Styx bensoin Dryand., Rhinoceros unicornis L., Lindera styrchnifolia, Syzygium aromaticum Merr et Perry, Aconitum carmichaeli Debx, Aconitum ciliare DC., Aquilaria agallocha Roxb., Piper longum L. | 4 (0.2)      |
| Cibotium barometz J. Smith, Sinapis alba L., Acanthopanax sessiliflorus, Psoralea corylifolia L., Scrophularia buergeriana Miq. | 3 (0.1)      |
| Oryza sativa L., Cervus nippon Temminck, mirabilite, Dolichos lablab L., Morus alba L., Perilla frutescens var. acuta Kudo, Gentiana scabra Bunge, Arctium lappa L., Prunus humilis Bunge, Lycium chinense Mill., Gentiana macrophylla Pall., Cuscuta chinensis Lam., Croton tiglium Miq., Fritillaria thunbergii Miq., Taraxacum platycarpum H. Dahlsh, Corydalis ternata Nakai | 2 (0.1)      |
| Alpinia officinarum Hance, Sophora flavescents Ait., Lycium chinense Mill., Prunus persica (L.) Batsch, Comminphora myrrha Engl., Bombyx mori L., Tribulus terrestris L., Rubus coreanus Miq., Spiridela polyphylla (L.) Schleid., Adenophora triphylla var. japonica Harra, Cryptotympana pustulata Fabricius, Prunus mume Sieb. et Zucc., Myristica fragrans Houtt., Artemisia capillaris Thunb., Uncaria sinensis (Oliv.) Havil., Gastrodia elata BL., Trichosanthes kirilowii Maxim., Amomum tsaoa Crevost et Lemaire, Uncinia kamtschatayi Hayata, Sesamum indicum L., Erodium stephanianum Willd. | 1 (0.0)      |
compared to the initial INR, and the ratio of adverse events were not significantly different between the herbal group and the nonherbal group. It is suggested that concurrent use of prescribed herbal medicine and warfarin may not influence INR value or bleeding tendency compared with conventional therapy.

Conflict of Interests

No author has any conflict of interests in this work.

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