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ORIGINAL ARTICLE

# Quantitative Analysis of Metal Contents in Korean Herbs and Herbal Products to Give Advice for Metal Allergic Patient

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**Background:** Herbs have been used worldwide as complementary and alternative medicines. In Korea, herbs for medical purpose are strictly controlled by the Korea Food and Drug Administration (KFDA). But it does not provide standards for metal antigens. **Objective:** This study conducted to identify the metal contents of Korean herbs and herbal products and to give information on counselling metal allergic patient. **Methods:** The concentration of three metal allergens with high antigenicity, cobalt (Co), chromium (Cr), nickel (Ni) was quantitatively determined using inductively coupled plasma with a mass spectrometer after nitric acid ($HNO_3$) digestion. The herbal objects are as follows: 1) ten kinds of herb plants, 2) ten herbal products sold in Korean drugstores, and 3) ten herbal extracts prescribed by Korean herbal doctors. **Results:** In 30 samples, Ni and Cr were detected in all items. Co was not detected in two drugstore products. **Conclusion:** Although the levels of metal detected in this study were very low relative to international guidelines and KFDA regulations, the herbal preparations contained similar or higher metal levels than known metal-rich foods. It can cause problems when it added to the daily diet and cause deterioration of skin lesions of metal sensitized person. **(Ann Dermatol 31(4) 414～419, 2019)**

**-Keywords-**
Complementary therapies, Dermatitis, contact, Herbal medicine, Metals

## INTRODUCTION

Herbs have been used worldwide as complementary and alternative medicines (CAMs) for thousands of years. Korea has traditionally used a variety of herbal products, and 85.5% of the Korean general population has used an herbal medicine more than once in their lifetime[1]. Herbs are cultivated and harvested in natural environments and, thus, are heavily influenced by metal contamination of the soil and surrounding environment. Therefore, many countries consistently analyze the metal contents of herbs and herbal products[2-5].

In Korea, herbs are categorized as 'food ingredients' when used as foodstuffs and 'herbal plants' when used for medicinal purposes. Herbal plants used by Korean herbal doctors, the Hospital of Oriental Medicine, pharmaceutical companies, pharmacies, and Oriental medicine dispensaries should meet quality-control standards based on the regulations of the Korea Food and Drug Administration (KFDA)[6-9]. However, the updated Korean herb and herbal-product purity guidelines include only four heavy metals, arsenic (As), lead (Pd), cadmium (Cd), and mercury (Hg), whereas other metals are measured as the sum of the total metals using the sulfide precipitation method.

In Korea, 43.6% of adverse reactions associated with Oriental medicines involve dermatological problems, which are the most common side effects[1]. For example, contact der-

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matitis, arsenic keratosis, phototoxicity, and alopecia have been reported after using herbal products[10]. Since the 2000s, countries around the world have noted that CAMs, including herbs, may be an important ingestion factor for metal antigens such as nickel, chromium, cobalt, and mercury[11-14]. However, no studies have investigated the metal contents of Korean herbs and herbal products with the potential to cause contact dermatitis. Therefore, this study aimed to identify the metal contents of Korean herbs and herbal products and to give information on counselling metal allergic patient compared with previous reports in literature reviews.

## MATERIALS AND METHODS

### Study materials

In this study, 10 herbal plants that are ranked among the top 10 most commonly used in Korea according to the 2010 Korea National Statistical Office Notice were obtained from a KFDA approved pharmaceutical company. Ten herbal products sold in Korean drugstores and 10 herbal extracts prescribed by Korean herbal doctors were purchased randomly.

### Study methods

After all solid samples were ground homogeneously, 0.5 g of sample was placed in Teflon container and mixed with 7 ml undiluted nitric acid ($HNO_3$). The mixture heated to 150°C and cooled to room temperature. After opening lid, the mixture was reheated to achieve a dry state. Next, 5 ml undiluted $HNO_3$ and 1 ml perchloric acid were added to the dry material and sealed. The mixture was thermally decomposed at 150°C, cooled to room temperature, reheated until it had dried, and then diluted with 1% $HNO_3$ to produce a total 50 ml.

For liquid samples, 1 ml of the liquid sample was placed in 60 ml Teflon container and mixed with 2 ml undiluted $HNO_3$. The mixture heated to 150°C and cooled to room temperature. After opening lid, the mixture was reheated to achieve a dry state and diluted with 1% $HNO_3$ to produce a total 50 ml.

The preprocessed samples were analyzed twice to measure the three metals: Cr, Ni and Co which could cause allergic contact dermatitis listed in Fisher's contact dermatitis 6th edition[15]. An inductively coupled plasma mass spectrometer (iCAP™ TQ ICP-MS®; Thermo Scientific, Bremen, Germany) was used to assess the herbal plants and herbal products sold in drugstores, whereas a different inductively coupled plasma mass spectrometer (X-SERIES ICP-MS®; Thermo Elemental, Winsford, UK) was used to assess the herbal extracts.

The analytical detection limits for the iCAP™ TQ ICP-MS® were as follows: 0.001 μg/kg for Cr, 0.001 μg/kg for Ni, 0.001 μg/kg for Co. The analytical detection limits for the X-SERIES ICP-MS® were 0.1 μg/kg for Cr, 0.2 μg/kg for Ni and 0.1 μg/kg for Co.

### Calculation of mean daily metal intake

To calculate the mean daily metal intakes from herbal plants and herbal extracts, either the daily intake doses that were described on the medicine packages or the daily intake directions described by Korean herbal doctors or pharmacists were used. The daily intake doses for herbal plants were calculated according to the mean daily intake doses suggested by the KFDA for evaluating hazards associated with herbal medicines in 2016 (Table 1)[16]. The KFDA study conducted for 174 kind of herbal material in total of 5,000 Korean distribution channels which trading herbs (oriental medicine, oriental medicine hospitals, oriental pharmacies, pharmacies and herbal medicine pharmacies) for 2 years. Total 62,741 herbal prescription and herbal item usage amount information had been collected by survey paper response or visiting survey[16].

## RESULTS

The results from the quantitative analyses of 30 herbal items, including herbal plants, herbal products, and herbal extracts, are shown in Table 2.

### Analytical results according to metal type

Ni was detected in all 30 items. The mean Ni content was 0.736 ppm (0.002～2.224 ppm) in herbal plants, 0.392 ppm (0.011～0.958 ppm) in herbal products sold in Korean drugstores, and 0.140 ppm (0.085～0.214 ppm) in herbal extracts. Thus, the mean daily Ni intake was 5.048 μg/d (0.011～14.275 μg/d) from herbal plants, 8.409 μg/d

**Table 1.** Mean daily intake dose of Korean herbs[16]

| Order | Items | Mean daily intake dose (g) |
|---|---|---|
| 1 | Herb A (*Angelica Gigas* root) | 6.42 |
| 2 | Herb B (*Poria*) | 6.84 |
| 3 | Herb C (*Astragalus* root) | 7.53 |
| 4 | Herb D (*Peony* root) | 6.29 |
| 5 | Herb E (*Licorice*) | 5.42 |
| 6 | Herb F (*Cnidium* rhizome) | 6.41 |
| 7 | Herb G (Prepared *Rehmannia* root) | 8.27 |
| 8 | Herb H (*Liriope* tuber) | 6.8 |
| 9 | Herb I (*Alisma* rhizome) | 7.3 |
| 10 | Herb J (*Bupleurum* root) | 6.3 |

**Table 2.** Metal content in Korean herbs, herbal products and herbal extracts

| Items | | Metal content (ppm) | | | Daily metal intake (μg) | | |
|---|---|---|---|---|---|---|---|
| | | Cr | Co | Ni | Cr | Co | Ni |
| I. Material (solid) | Herb A (*Angelica Gigas* root) | 1.582 | 0.413 | 2.224 | 10.155 | 2.654 | 14.275 |
| | Herb B (*Poria*) | 0.020 | 0.052 | 0.002 | 0.136 | 0.352 | 0.011 |
| | Herb C (*Astragalus* root) | 2.234 | 0.059 | 1.308 | 16.822 | 0.448 | 9.850 |
| | Herb D (*Peony* root) | 1.351 | 0.052 | 0.760 | 8.496 | 0.324 | 4.783 |
| | Herb E (*Licorice*) | 0.522 | 0.058 | 0.334 | 2.832 | 0.315 | 1.812 |
| | Herb F (*Cnidium* rhizome) | 0.366 | 0.091 | 0.253 | 2.349 | 0.582 | 1.621 |
| | Herb G (Prepared *Rehmannia* root) | 3.685 | 0.331 | 1.021 | 30.478 | 2.739 | 8.447 |
| | Herb H (*Liriope* tuber) | 2.959 | 0.078 | 0.409 | 20.118 | 0.531 | 2.780 |
| | Herb I (*Alisma* rhizome) | 0.485 | 0.090 | 0.309 | 3.543 | 0.657 | 2.255 |
| | Herb J (*Bupleurum* root) | 2.225 | 0.174 | 0.738 | 14.019 | 1.094 | 4.648 |
| II. Final product (solid) | Herbal product F (Danggwisusan Extract Granules) | 0.270 | 0.069 | 0.502 | 2.431 | 0.620 | 4.516 |
| | Herbal product G (Socheongryongtang Mix Extract Powder) | 0.360 | 0.114 | 0.468 | 3.242 | 1.024 | 4.215 |
| | Herbal product H (Eungyosan Extract Granules) | 0.462 | 0.082 | 0.958 | 4.157 | 0.738 | 8.620 |
| | Herbal product I (Banhasasimtang Mix Extract Powder) | 0.239 | 0.091 | 0.437 | 2.150 | 0.823 | 3.932 |
| | Herbal product J (Insampaedogsan Mix Extract Powder) | 0.996 | 0.066 | 0.652 | 8.963 | 0.593 | 5.865 |
| | Herbal product E (Jeongrohwan Pill) | 0.547 | 0.120 | 0.658 | 0.984 | 0.215 | 1.184 |
| III. Final product (liquid) | Herbal product A (Ssanghwatang Extract Solutions) | 0.003 | 0.015 | 0.074 | 0.860 | 4.430 | 22.166 |
| | Herbal product B (Gaswhalmyungsu Solution) | 0.041 | Bdl | 0.011 | 9.113 | NE | 2.377 |
| | Herbal product C (Hyanggaltang Extract Solutions) | 0.020 | 0.012 | 0.076 | 6.105 | 3.674 | 22.822 |
| | Herbal product D (Uhwangcheongsimwon Solution [Altered Prescription]) | 0.113 | Bdl | 0.084 | 11.268 | NE | 8.394 |
| IV. Herbal extract (liquid) | Herbal extract A | 0.002 | 0.016 | 0.130 | 0.728 | 4.724 | 39.024 |
| | Herbal extract B | 0.009 | 0.013 | 0.214 | 2.695 | 4.028 | 64.296 |
| | Herbal extract C | 0.005 | 0.009 | 0.103 | 1.390 | 2.818 | 30.960 |
| | Herbal extract D | 0.009 | 0.015 | 0.145 | 2.766 | 4.418 | 43.524 |
| | Herbal extract E | 0.007 | 0.018 | 0.159 | 1.981 | 5.308 | 47.616 |
| | Herbal extract F | 0.007 | 0.020 | 0.154 | 2.153 | 6.005 | 46.164 |
| | Herbal extract G | 0.008 | 0.024 | 0.139 | 2.480 | 7.130 | 41.604 |
| | Herbal extract H | 0.007 | 0.021 | 0.141 | 2.154 | 6.191 | 42.324 |
| | Herbal extract I | 0.005 | 0.011 | 0.085 | 1.463 | 3.258 | 25.416 |
| | Herbal extract J | 0.008 | 0.020 | 0.131 | 2.383 | 6.101 | 39.192 |

Bdl: below detection limit, NE: not estimated.

(1.184～22.822 μg/d) from herbal products sold in Korean drugstores, and 42.012 μg/d (25.416～64.296 μg/d) from herbal extracts. Of the 10 herbal extracts, 1 in particular (Herbal extract B) had a mean daily Ni intake of 64.296 μg/d, and 6 had a daily mean intake greater than 40 μg/d.

Cr was detected in all 30 samples. The mean Cr content was 1.543 ppm (0.020～3.685 ppm) in herbal plants, 0.305 ppm (0.003～0.996 ppm) in herbal products sold in Korean drugstores, and 0.007 ppm (0.002～0.009 ppm) in herbal extracts. Thus, the respective mean daily Cr intakes were 10.895 μg/d (0.136～30.478 μg/d), 4.927 μg/d (0.860～11.268 μg/d), and 2.019 μg/d (0.728～2.766 μg/d). A Cr content higher than 0.7 ppm was observed in six herbal plants and one herbal product sold in Korean drugstores.

Co was detected in all study samples except two herbal products sold in Korean drugstores. The mean Co content was 0.140 ppm (0.052～0.413 ppm) in herbal plants, 0.057 ppm (up to 0.120 ppm) in herbal products sold in Korean drugstores, and 0.017 ppm (0.009～0.024 ppm) in herbal extracts. Thus, the respective mean daily Co intakes were 0.970 μg/d (0.315～2.739 μg/d), 1.212 μg/d (up to 4.430 μg/d), and 4.998 μg/d (2.818～7.130 μg/d). Mean daily Co intake greater than 6 μg/d was found from four herbal extracts.

### Characteristics according to material (herbal plant) and finished product (herbal product and extract)

Herbal plants had higher mean metal contents for all metals than those of herbal products and herbal extracts (mean metal contents of herbal plants, Cr 1.543 ppm, Co 0.140 ppm, Ni 0.736 ppm). The lowest mean metal content was detected in herbal extracts (mean metal contents of herbal extracts, Cr 0.007 ppm, Co 0.017 ppm, Ni 0.140

ppm). However, when this value was converted to mean daily metal intake, Co levels were 5.15 times higher, Ni levels 8.32 times higher in herbal extract than the herbal plants (mean herbal extracts daily intake Co 4.998 μg, Ni 42.012 μg; mean herbal plants daily intake Co 0.970 μg, Ni 5.048 μg).

## DISCUSSION

As CAM use broadens worldwide, and the international market expands rapidly, emphasis on the safety and quality of herbs and herbal products is increasing[17]. According to the World Health Organization (WHO), herbal products were regulated in 65 countries in 1999 but in as many as 119 in 2012[18].

In Korea, various herbal products are used in medical institutions such as the oriental medicine hospitals, pharmacies, as well as in the private sector in functional foods, teas, and spices. The regulation of heavy metals in herbal products was strengthened in April 2006 in Korea, and the limits of four metals (Pb ≤5 ppm, As ≤3 ppm, Cd ≤0.3 ppm, and Hg ≤0.2 ppm) were incorporated into previous regulations recommending total amounts ≤30 ppm. Because most final herbal extracts and products prescribed by Korean herbal doctors consist of several raw herbal plant materials, herbal extracts and products may have metal levels several times higher than each herbal plant components. In this study, ingesting some herbal extract led to daily metal intake values up to 22.63 times higher Co and up to more than five thousand times higher Ni than for ingesting an herbal plant (Table 2). However, herbal plants and specific herbal products listed in the KFDA are regulated in Korea, whereas herbal products prescribed by Korean herbal doctors are not. Same regulation limit applies to herbal plants, which are raw materials, and herbal products, the final products. In contrast to the Korean Pharmacopoeia (KP), Canada and USA apply stricter regulations to final products than raw materials[19]. Although the regulations on herbal products have been strengthened, these regulations refer only to certain heavy metals, and there have been no standards for evaluating metals as allergens until now.

Fortunately, most of the herbal plants and products analyzed in this study had little metals relative to permissible tolerable daily intake levels provided by several international organizations (Table 3).

Ni is a ubiquitous element with strong antigenicity, and Ni allergies are generally reported in 10% to 20% of the population. Food and water are the primary sources of Ni exposure. The level of dietary Ni intake varies from 20 to 600 μg/d, depending on the geographic area[15,20,21]. A strong correlation has been observed between the amount of ingested Ni and allergic contact dermatitis. Dietary interventions, including Ni restriction, are important for treatment and prevention of Ni allergy, because very low concentrations (10～60 μg/kg) can elicit allergic reaction after sensitization[20,22,23]. Well-known Ni-rich foods include cocoa, peanuts, and chocolate. Jacob et al.[24] reported that four Ni allergic children who improved after strict Ni restriction diet showed abrupt deterioration after eating chocolate bars, and Krecisz et al.[14] reported a case of systemic contact dermatitis following cocoa ingestion[23-25]. In these two reports, Ni in the food was approximately 50 μg (50 g/chocolate bar, 1.00 [0.85～1.32] mg/kg Ni[24]; 5 g/recommended daily dose of cocoa powder, 10 mg/kg Ni[26]). In this study, six herbal extracts had daily Ni intake similar to or higher than 50 μg (Table 2). Han et al.[25] analyzed Ni content of Korean foods in 2005 and found considerably more Ni in most Korean foods than previous reports. For example, the Ni content of Korean green tea bags is 7,852 times higher than that reported by Veien and Andersen[26] in 1986[25]. Fortunately, the Ni contents of herbal plants and products in this study were considerably lower than those previous reported from other countries[2,3,27-31]. However, the metal contents of herbal plants and products can differ greatly, even in the same country, depending on types of selected herbal plants, cultivation environment, and time obtained[2,29]. Thus, interpretations

**Table 3.** Permissible tolerable daily intake (PTDI)

| Metal | PTDI |
|---|---|
| Chromium (Cr) | not evaluated (JECFA), 0.15 mg Cr(III)/kg/d (UK EVM), 0.9 μg Cr(IV)/kg/d (WHO/IPCS), 300 μg Cr/kg/d (VKM), 250 μg Cr/d (WHO/IPCS) |
| Cobalt (Co) | - |
| Nickel (Ni) | 6.0 μg Ni/kg/d (US EPA), 5 μg Ni/kg/d (FAO/WHO) |

JECFA: Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives, UK EVM: United Kingdom Expert Group on Vitamins and Minerals, WHO: World Health Organization, IPCS: International programme on chemical safety, VKM: Norwegian Scientific Committee for Food and Environment, US EPA: United States Environmental Protection Agency, FAO: Food and Agriculture Organization.

of these results should be careful[2,3,27-31].

Cr is commonly used in alloys and showed sensitization rate up to 6%[32]. Irritant dermatitis, dyshidrotic eczema, and contact dermatitis are closely related to dietary or medicinal Cr. Fregert and Rorsman[33] reported that a provocation test using 50 μg oral dichromate salt in five Cr allergy patients caused acute flare-ups of hand eczema. Korean herbal products contain average Cr of 0.618 ppm, which is six times higher than daily diet (0.1 ppm)[34]. In this study, six herbal plants and one herbal product contained five times more Cr than nuts (0.7 ppm), a well-known Cr-rich food[35]. One herbal plants, Herb G (prepared *Rehmannia* root) contained 3.685 ppm (Table 2).

Co exposure commonly occurs via inhalation, oral ingestion, and contact and can cause irritant dermatitis, contact dermatitis, allergic vasculitis, and hand eczema (dyshidrotic eczema)[36]. Like Ni, geographic and environmental conditions affect Co contents of food and water[37]. Stuckert and Nedorost[36] suggested that $<12$ μg/d is appropriate for standard Co-restricted diet. In this study, four herbal extracts had Co levels higher than 50% of the restricted diet standard, and one (Herbal extract G, 7.13 μg/d) had up to 60% (Table 2).

In Korea, many patients use CAMs to treat allergic diseases such as asthma, rhinitis, atopic dermatitis, and urticaria[1]. But significant levels of high-antigenicity metals, such as Ni, Co and Cr are contained in Korean herbal plants and products compared with the metal levels in Ni- or Cr-rich foods which can aggravate metal allergy patient or those of Co-restricted diets.

In addition to the metals assessed in this study, other studies have reported that CAMs contain manganese, iron, zinc, and selenium. Assessments of these metals in Korean herbal products should be conducted in the future[4,30].

When describing metal-restricted diets, most authors distinguish between metal-rich and low-metal foods based only on metal content. However, in addition to content, actual dietary intake amount is an important factor for metal exposure. Dietary intake should be taken into consideration in dietary education. In this study, the lowest mean metal content was detected in herbal extracts compared with herbal plants and products sold in Korean drugstores. However, when the contents were converted to daily intake values, there was 5.15 times higher in Co and 8.32 times higher in Ni daily metal intake from herbal extracts than from herbal plants.

The present study is limited in that it involved a small sample number and purchased only in Seoul. Furthermore, because all of the samples were KFDA-approved, these results do not represent the herbs obtained from markets.

In previous analyses of Korean herbs, only certain heavy metals (Pb, As, Cd, and Hg) in raw herbal plant were assessed. Therefore, this study was the first to analyze metal antigens in Korean herbal plants and the final ingested forms of herbal products. The herbal preparations contained similar or higher metal than known metal-rich foods. The KFDA has strict regulations on heavy metals, pesticide, and aflatoxins but does not provide standards for metal antigens. The allergenicities of herbal products have been underestimated. Metal exposure differs depending on the intake amount, and place of purchase, even for the same herb. Therefore, doctors should perform a detailed medical history about the usage of herbal products and the place of purchase for patients with intractable contact dermatitis or acute deteriorated lesions.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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