ORIGINAL ARTICLE

Quality Assessment of Cut Crude Drugs Using the Checksheet Incorporating Minimum and Maximum Marker Constituent Contents

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ABSTRACT

Aims: **Traditionally, Kampo practitioners have relied on the five senses to carry our quality evaluation of cut crude drugs. In a previous paper, we reported on an investigation into eight cut crude drugs (Ephedra Herb, Coptis Rhizome, Rhubarb, Scutellaria Root, Peony Root, Magnolia Bark, Phellodendron Bark, Moutan Bark) purchased by the Kitasato University Oriental Medicine Research Center (OMRC). In that investigation, we used the test data provided by the supplier for the relevant lots to compare marker ingredient amounts with those stipulated in The Japanese Pharmacopoeia (JP) and to ascertain fluctuations in the ingredient amounts between lots for each of the drugs, which we expressed in terms of a fluctuation index (CV). We developed a checksheet to help practitioners conduct a more thorough evaluation of cut crude drugs than is possible through use of the five senses alone, where a CV of greater than 10% is considered to be a significant change in the profile of the cut crude drugs. In the present prospective study, we attempt to determine the feasibility of the method and develop recommendations for JP.**

Methods: **The present investigation was conducted with the same eight cut crude drugs, including all the lots used at the OMRC from the year 2007 to the year 2011. Using the test data provided by the supplier, we checked the ingredient amount for marker ingredients Total Alkaloids, Berberine, Sennoside A, Baicalin, Paeoniflorin, Magnolol, Berberine, and Paenol. We also considered the utility of the checksheet and its prospects for use in future practice.**

Results: **Using the checksheet, we were able to show changes over time in ingredient amounts for the eight cut crude drugs in question. Although results differed depending on the drug, fluctuations were generally within the acceptable limits.**

Conclusion: **For most of the drugs listed in The Japanese Pharmacopeia, only lower limits are specified for the quantities of marker ingredients. This is inadequate from the point of view of ensuring consistent treatment. We developed a checksheet designed to aid Kampo practitioners and demonstrated its usefulness. We hope for a revision of JP that takes greater account of the realities of clinical use.**

KEY WORDS

cut crude drugs, quality assessment, The Japanese Pharmacopoeia, index constituent amount, medical institution, adoption of standards, checksheet-based quality assessment

INTRODUCTION

Kampo Medicine is an ancient medical practice in which herbs are blended to relieve various conditions. Originally, it was called herbalism, and its principles and various herbal formulae were compiled during the Han Dynasty in the work *Shennong Bencaojing* (Shennong's Classic of Materia Medica). In the subsequent centuries, a variety of books of herbalism were written, with the aims of establishing which purported effects of herbal materials were real, what beneficial and harmful qualities each herb possessed, and how each herb should be used according to what principles[1]. One key principle established to guide the appropriate use of herbs was that of the five flavours (pungent, sour, sweet, bitter, and salty). This principle appears to have been linked to the five phases (wood, fire, earth, metal, and water) theory of Chinese philosophy and to have contributed to ancient Chinese nutritional science as well as aiding in quality evaluation of herbs. In accordance with this tradition, evaluation of herbs is still generally performed based on the five senses (sight, hearing, touch, taste, and smell).

The first edition of The Japanese Pharmacopoeia (JP), published on May 20th, 1886, referred to the taste and smell of herbs[2]. That practice has continued to this day and can be observed in the current 18th edition[3], suggesting that taste and smell are still useful indicators of drug quality. Anjiki *et al*. have conducted objective measurement using taste sensors of Kampo herbs, but as yet there are no generally accepted standards[4]. This means that the burden of evaluation lies with each medical

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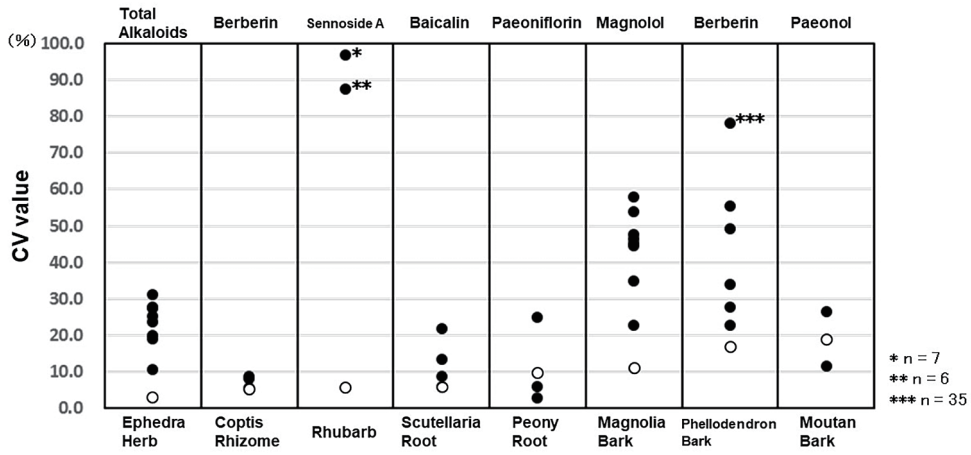

Figure 1: CV values indicating variation between cut crude drug lots

Comparison between previously established marker constituent amounts (as stated by manufacturers [8,9] or in existing literature [10-16]) (●) and amounts found in lots delivered to OMRC previously established amounts : amounts found at OMRC (○)

Table 1: Average and Reference width of crude drugs between product lots

A reference range was established from the mean and standard deviation of the component content in each crude drug.

Crude drugs	Ingredient	Standard value (%)	Average (%)	Reference width (max. ～ min.) (%)
Coptis Rhizome	Berberine	More than 4.2	6.09	6.40 ～ 5.77
Ephedra Herb	Total Alkaloids	More than 0.7	1.24	1.27 ～ 1.20
Magnolia Bark	Magnolol	More than 0.8	3.02	3.35 ～ 2.69
Moutan Bark	Paeonol	More than 1.0	1.95	2.09 ～ 1.82
Peony Root	Paeoniflorin	More than 2.0	3.27	3.49 ～ 3.06
Phellodendron Bark	Berberine	More than 1.2	3.84	4.24 ～ 3.43
Rhubarb	Sennosides A	More than 0.25	0.92	0.97 ～ 0.87
Scutellaria Root	Baicalin	More than 10.0	17.51	18.55 ～ 16.48

institution that uses crude drugs, and it is difficult to know how well they are doing it.

In an earlier study, we investigated the amounts of the marker constituents Total Alkaloids, Berberine, Sennoside A, Baicalin, Paeoniflorin, Magnolol, Berberine, and Paenol contained in the cut crude drugs Ephedra Herb, Coptis Rhizome, Rhubarb, Scutellaria Root, Peony Root, Magnolia Bark, Phellodendron Bark, and Moutan Bark used in the Kitasato University Oriental Medicine Research Center (OMRC), comparing those amounts to those stipulated in the 14th edition of JP[5]. Using the test data provided by the suppliers for each lot, we calculated a fluctuation index (CV) for each marker constituent to show how much the amount changed between lots[6,7]. It was calculated according to the following formula based on the standard deviation (SD) of constituent amounts between lots and the average amount(μ):

$CV\ (\%) = SD \div \mu \times 100$

Our investigations showed that the CV values for the crude drugs used at OMRC tended to be lower than would be expected based on those published elsewhere and that fluctuations between lots were comparatively low (Figure 1)[8-16].

The use of CV values to compare marker constituent amounts between cultivars has been reported[17] but so far we have not found reports of their use in quality evaluation. Therefore, the present study, taking a CV of 10% as acceptable variation, prospectively investigates the usefulness and feasibility of the checksheet developed by us (Table 1, Figure 2)[7] for checking the quality of crude drugs in clinical practice. Since stringent quality control has ecological implications (excessively narrow bounds of variation in marker constituent content might require the dumping of otherwise good-quality drugs), it is important to ascertain whether the 10% value is reasonable in clinical practice.

MATERIALS AND METHODS

The cut crude drugs used in this study are Ephedra Herb, Coptis Rhizome, Rhubarb, Scutellaria Root, Peony Root, Magnolia Bark, Phellodendron Bark, and Moutan Bark. We referred to the 14th edition of JP for the criteria with respect to the amounts of Total Alkaloids, Berberin, Sennoside A, Baicalin, Paeoniflorin, Magnolol, Berberine, and Paenol expected to be present in the herbs, and checked the amounts present according to the test data for each lot provided by the supplier[5]. During the period of investigation, Phellodendron Bark and Moutan Bark were supplied by Tochimoto Tenkaido Co., Ltd. Ephedra Herb, Coptis Rhizome, Rhubarb, Scutellaria Root, Peony Root, and Magnolia Bark were supplied by Uchida-wakanyaku Ltd.

Between 2007 and 2011, we recorded the amounts of marker constituents on every lot of the drugs above obtained by OMRC. We conducted a prospective investigation of the usefulness and feasibility of the checksheets we developed to systematize drug evaluation.

RESULTS

For Ephedra Herb, Coptis Rhizome, Rhubarb, Scutellaria Root, Peony Root, Magnolia Bark, Phellodendron Bark, and Moutan Bark, by inspecting the test data for each lot, we investigated the change over time in the amounts of marker constituents.

For Ephedra Herb, we found a slight decrease over time in the amount of Total Alkaloids (Figure 3 (a)). For Coptis Rhizome, we found a slight increase over time in the amount of Berberine (Figure 3(b)). For Rhubarb, we found that the amount of Sennosides A decreased to the lower limit but then remained stable (Figure 3(c)). For Scutellaria Root, the amount of Baicalin started near the lower limit but then approached the middle of the acceptable range (Figure 3(d)). For Peony Root, the amount of Paeoniflorin decreased gradually (Figure 3(e)). For Magnolia Bark, the amount of Magnolol remained constant (Figure 3(f)). For Phellodendron Bark, the amount of Berberine fluctuated slightly (Figure 3(g)). For Moutan Bark, the amount of Paeonol fluctuated within the acceptable range (Figure 3(h)).

Overall, although each drug was different, the fluctuations of marker constituent amounts were within the acceptable bounds we estab-

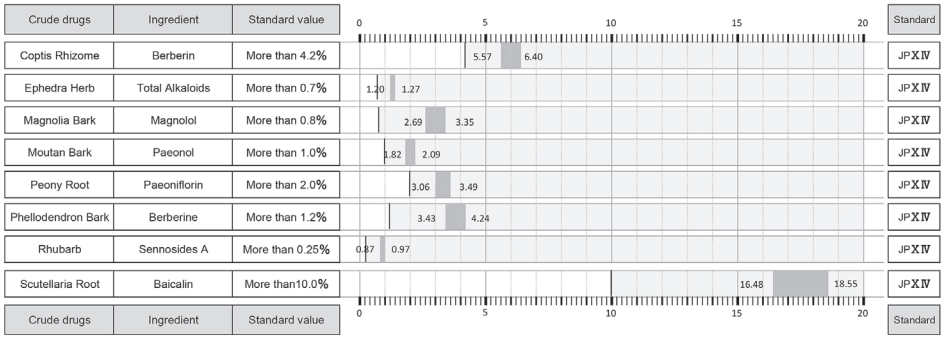

Figure 2: Quality assessment checksheet (marker constituent amount)

For each crude drug, the JP XIV standard component content values are indicated by solid lines, and the lower and upper limits of the actual measured values obtained from the product lot and our standard range are indicated by shaded bands. This check sheet is used to ensure that the product falls within the standard range when selecting the same crude drug. Standard values are as stipulated in the Japanese Pharmacopoeia 14th edition.

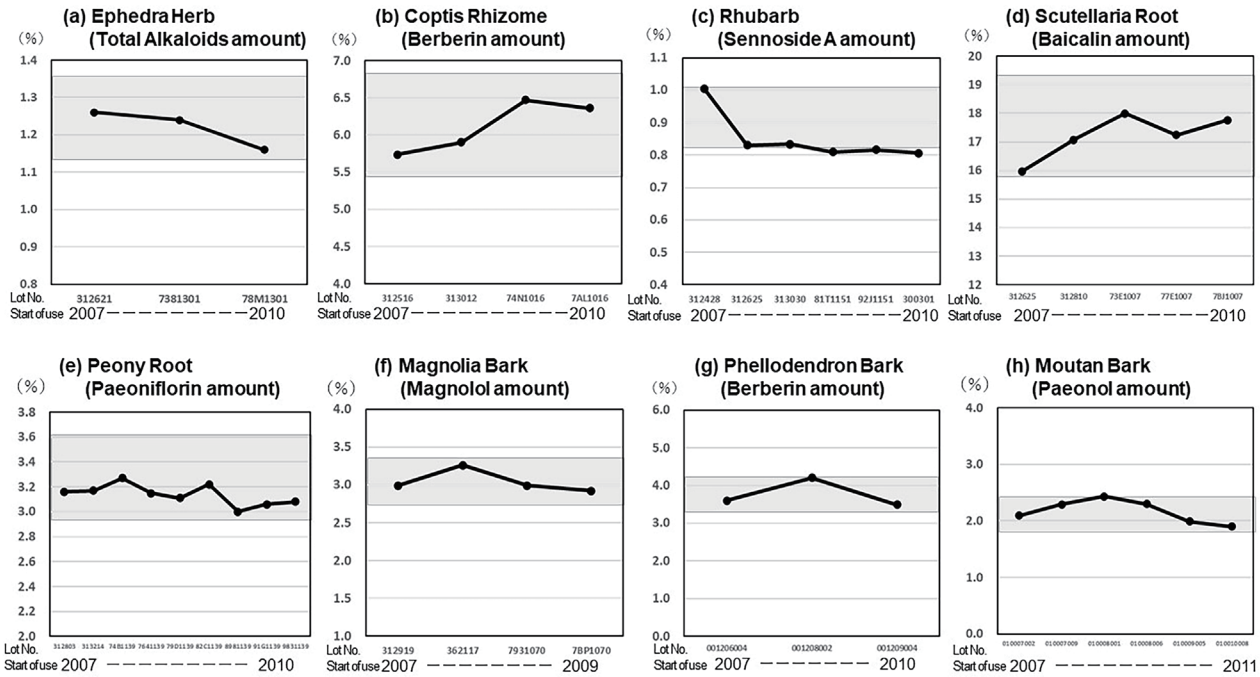

Figure 3: Fluctuation in marker constituent amounts between lots for each herb after determination of the standards

Horizontal axis shows the lot number and the date when use of that lot began. The shaded areas represent the standard ranges used.

(a) Ephedra Herb (Total Alkaloids amount), (b) Coptis Rhizome (Berberine amount), (c) Rhubarb (Sennosides A amount), (d) Scutellaria Root (Baicalin amount), (e) Peony Root (Paeoniflorin amount) , (f) Magnolia Bark (Magnolol amount), (g) Phellodendron Bark (Berberine amount), (h) Moutan Bark (Paeonol amount)

lished.

DISCUSSION

Although there have been several attempts to evaluate crude drug quality objectively, none has been adopted by JP, and it appears that none has been adopted in clinical practice[18-23].

The General Information section of JP states: Referring to the biosynthesis of natural products, the content of these compounds specified as marker constituents are unlikely to be independently changed to stand out from others. The specification values of crude drugs and crude drug preparations are stipulated in order to control the appropriate production process based on the strategy that every crude drug and crude drug preparation will be standardized to a certain level through the content control of marker constituents[24].

It is therefore reasonable to conclude that the amount of the marker constituents present in drug lots is a suitable way to evaluate drug quality. However, for most constituents, there is only a lower limit, and no upper limit has been established[3]. In our view, this is insufficient from the point of view of reproducibility of treatment in clinical settings.

Thus, our checksheet, by establishing 10% as acceptable CV values, based on contents of marker ingredients in actual drug lots, deal not only with minimum but also maximum values. We investigated prospectively whether the 10% criterion would be feasible and usable in clinical practice. The results suggest that it is and, more generally, that use of the marker constituent amounts stipulated in JP for quality evaluation is valuable.

If a clinical practice should obtain a lot where the content of marker constituents goes outside the standards, it might be appropriate to reconsider the purchase; alternatively, such information could be communicated to practitioners so that they can make appropriate adjustments in the quantity of drug to be used and avoid harm to patients, ensuring consistency and reproducibility of treatment.

CONCLUSION

The results of the present study show that use of our checksheet based on CV values that indicate acceptable bounds of fluctuation in marker constituent contents of crude drug lots is feasible and meaningful for ensuring consistency and reproducibility of treatment, and that there may be no need to rely on the traditional method based on the five senses. We believe that our method can be adopted at other medical institutions.

Setting acceptable bounds of fluctuation in marker constituent contents of crude drugs is a promising direction, and it is our hope that this innovation will be adopted in future by the JP.

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CONFLICT OF INTEREST

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