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# Variation of Heavy Metal Content of Market Variants of Ayurvedic Formulation - Lack of Good Manufacturing Practices (GMP)

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors VG and PB designed the study, wrote the protocol, and managed the literature searches. Authors VG, AL and PB managed the analyses of the study. Author RB wrote the first draft of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aim:** The present study was conducted to estimate the heavy metal content in samples of Kutazghan Vati (a pill), from three different manufacturers to know about the quality control measures being followed by manufacturers for GMP. The study will also provide a platform for regulatory authorities to tighten the noose and upgrade the industry about high heavy metal levels in relation to international regulations.
**Methodology:** Three variants of Kutajghan Vati coded as A, B, and C manufactured by different leading manufacturers was procured from local market. Heavy metals analysis was done according to AOAC (1995) for non volatile heavy metals.
**Results:** Cadmium content of two variants A and C was within permissible limits where as cadmium content of variant B was 2.98 ppm about ten times higher than the permissible limits of 0.3 ppm set up by WHO and the Ayurvedic Pharmacopoeia of India. The lead content of variant A was 36.33 ppm that was about four times against the permissible value set up by WHO. Despite very low detection limits, mercury and arsenic were not detectable in all the three variants depicting that the formulation were free from these heavy metals.
**Conclusions:** Despite same guidelines issued by same regulatory authorities for

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production of ayurvedic formulations for permissible limits of heavy metal content, three different manufacturers marketed the same formulation with different heavy metal content which reflects that industry seems to be negligent for maintaining proper quality control. This study suggests that periodic estimation of heavy metals is highly essential for single drugs, raw drugs as well as finished products for quality assurance and safer use of herbal drugs.

*Keywords: Heavy metals; quality assurance; herbal drugs; permissible limit.*

## 1. INTRODUCTION

Despite a worldwide growth of modern medicine a major chunk constituting about 80% of world population still relies on a traditional system of medicine based on herbal drugs. Herbal drugs constitute an essential component of traditional medicine in several developing countries including China and India. India has a well-established system of medicine known as Ayurveda that utilizes plants, animal and minerals for the welfare of human beings [1,2]. These plants and plant drugs have different chemical composition due to influence of climatic conditions, nature and properties of soil and fertilizer, geographical distribution, age of the plant, source of collection, altitude, period of harvesting, manufacturing practices etc [3]. Due to involvement of so many deciding factors, quality control of ayurvedic medicines has become a tedious and difficult task. In older times, the herbal drugs were prepared according to the requirement of the patient, but due to changed scenario herbal medicines are being manufactured on the large scale in pharmaceutical units, where manufactures come across many problems such as availability of good quality raw material, authentication of raw material, availability of standards, proper standardization methodology of single drug and formulations, quality control parameters etc. So today, there is a great need of standardization and quality control of ASU formulations. Medicinal plants have been the major source of the raw materials for the pharmaceutical industry. Indeed, about 25% of the prescription drugs dispensed in the United States contain at least one active ingredient derived from plant material. The safety and efficacy of herbal medicine is closely related with the quality of the source materials used in production.

Heavy metals are important environmental pollutants and many of them are toxic even at very low concentrations. In the past few decades due to rapid urbanisation and industrialisation, concentrations of these metals has increased in all major components of environment like soil, water and air [4] and at many places toxic levels have been reported. Monitoring of toxic heavy metals in herbs has recently been reported in different parts of the world [5,6,7] however a very little work has been done on estimation of heavy metals in finished products [8,9]. According to a 1990 study on ayurvedic medicines in India, 41% of the products tested contained arsenic, and 64% contained lead and mercury [10]. A 2004 study found toxic levels of heavy metals in 20% of ayurvedic preparations made in South Asia and sold in the Boston area, and concluded that ayurvedic products posed serious health risks and should be tested for heavy metal contamination [8]. A 2008 study of more than 230 products found that approximately 20% of remedies purchased over the internet from both US and Indian suppliers contained lead, mercury or arsenic [9].

Keeping this in view, the present study was conducted to estimate the heavy metal content in samples of Kutazghan Vati (a pill), from three different manufacturers. The study will also

provide a platform for regulatory authorities to tighten the noose and upgrade the industry about high heavy metal levels in relation to international regulations.

Kutajghan vati a widely used herbal drug is an ayurvedic anti-dysentery preparation which is also useful in many skin diseases [11,12]. Kurchicin is an active principle of Kutaj (*Holarrhena antidysenterica*), highly effective against causative microorganisms of diarrhoea and dysentery, especially for amoebic type [13].

## 2. MATERIALS AND METHODS

### 2.1 Sample Collection and Processing

Three variants of Kutajghan Vati coded as A, B, and C manufactured by different leading manufacturers was procured from local market. Table 1 shows the plant composition of the formulation with botanical name and the part of the plants used. The samples (about 500g) were kept at room temperature in the plastic food grade containers till complete analysis of samples.

**Table 1. Ingredients of Kutajghan vati**

| S. No. | Common name | Botanical name | Part used |
|---|---|---|---|
| 1. | Kurchi | *Holarrhena antidysenterica* L.(Wall) | Bark |
| 2. | Atish | *Aconitum heterophyllum* L.(Wall). | Whole plant |

### 2.2 Analysis

Heavy metals analysis was done according to AOAC (1995) for non volatile heavy metals [14]. For this 1.0 g powder of each sample was digested in $HNO_3$ and $HClO_4$ (9:1) using the wet digestion method by heating slowly on a hot plate under the fume hood chamber till a clear solution was obtained. The final volume was made up to 25 ml with deionised water. All necessary precautions were adopted to avoid possible contamination of the samples. Analysis was done by using Atomic Absorption Spectrophotometer. The standard reference material of all the metals (E. Merck) was used to provide calibration and quality assurance for each analytical batch. The efficiency of digestion of samples was determined by adding standard reference material of metals (E. Merck) to different samples. After addition of standards, samples were digested and metals were estimated as described above. Analytical recovery of the method has been checked by a parallel analysis of the two certified reference materials. Replicate analysis (n = 3) was conducted to assess precision of the analytical techniques.

#### 2.2.1 Estimation of As and Hg

Cold digestion for volatile heavy metals was followed and the method was developed and standardized in the laboratory [15]. Weighed powdered sample (0.1 g) was digested in Erlenmeyer flask (100 ml) and the flask was left overnight after adding 10 ml of conc. Sulphuric acid. It was then incubated at 70ºC in a water bath for one hour. The flask was then placed in an ice bath with constant shaking saturated aqueous potassium permanganate solution was added slowly. The process was continued till the colour of the permanganate persisted. After the flask reached room temperature, one ml of hydroxylamine hydrochloride 20 %w/v in distilled water) was added to reduce excess potassium

permanganate. This solution was made to desired volume by deionized water and used for estimation of As and Hg.

## 3. RESULTS AND DISCUSSION

Heavy metals namely cadmium, arsenic, mercury and lead were checked in these samples and the results are shown in Table 2. Cadmium content of two variants A and C was within permissible limits where as cadmium content of variant B was 2.98ppm about ten times higher than the permissible limits of 0.3ppm set up by WHO (1998) and the Ayurvedic Pharmacopoeia of India (2007) [16,17]. The lead content of variant A was 36.33ppm that was about four times against the permissible value set up by WHO (1998). Despite very low detection limits, mercury and arsenic were not detectable in all the three variants depicting that the formulation were free from these heavy metals. WHO/FDA has given the permissible limits of As, Hg, Pb and Cd in herbal drugs i.e. 10ppm, 1ppm, 10ppm and 0.3ppm respectively. Often because of commercial pressures, manufacturers resort to outsourcing of raw material leading to poor quality of the drugs. Failure of two formulation samples for the permissible heavy metals content demonstrates that the manufactures must not have followed good manufacturing practices and at the same time it is clear that the drugs were pumped without any quality check for heavy metal content. It is also possible that the raw material must have been obtained from contaminated and polluted areas and the herb collectors are not trained and there was no careful selection of site. Hence periodic assessment of heavy metals in finished product may not only help in avoidance of toxic effects due to heavy metals but may also help the pharmaceutical industry to follow stringent measures for quality assurance of herbal drugs with respect to cultivation practices, site selection, collection practices and good manufacturing practices.

**Table 2. Heavy metal concentrations in different market variants of Kutajghan Vati**

| S. No | Formulation code | Cadmium (ppm) | Lead (ppm) | Mercury (ppm) | Arsenic (ppm) |
|---|---|---|---|---|---|
| 1. | A (n=3) | 0.14 ±0.009 | 36.33 ±2.97 | ND | ND |
| 2. | B (n=3) | 2.84 ±0.160 | 2.84 ±0.19 | ND | ND |
| 3. | C (n=3) | 0.04 ±0.003 | 3.62 ±0.26 | ND | ND |
| 4. | WHO Permissible limit | 0.30 | 10.0 | 1.0 | 10.0 |
| 5. | Detection limit | 0.05 | 0.10 | 0.1 | 0.05 |

*ND-Not detected, n= number of replicates of the formulation*

## 4. CONCLUSION

Despite same guidelines issued by same regulatory authorities for production of ayurvedic formulations for permissible limits of heavy metal content, three different manufacturers marketed the same formulation with different heavy metal content. It shows that industry seems to be negligent for maintaining proper quality control. It has been concluded from this study that periodic estimation of heavy metals is highly essential for single drugs, raw drugs as well as finished products for quality assurance and safer use of herbal drugs.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

Not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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