Vol-3, Issue-5 PP. 355-361 ISSN: 2394-5788

GLOBAL JOURNAL OF ADVANCED RESEARCH
(Scholarly Peer Review Publishing System)

DOCUMENTATION OF CLINICAL SAFETY OF AYURVEDIC CLASSICAL FORMULATIONS WITH SPECIAL REFERENCE TO AROGYAVARDHINIGUTIKA

Dr. Tripathi S & Dr. Pandey S D
Shri Dhanwantry Ayurvedic College,
Sector 46B, Chandigarh – 160017,
India

Dr. Sastry J L N & Dr Sasibhushan V
Dabur Research & Development Centre,
Sahibabad - 201010 Ghaziabad, UttarPradesh,
India

ABSTRACT
Herbomineral formulations such as Arogyavardhinigutika have been used for liver and skin disorders in the Ayurvedic system of medicine. However, toxicity due to the presence of heavy metals in traditional medicines is a matter of concern and there have been reports questioning safety of their metallic contents, especially the presence of heavy metals. It, therefore, becomes imperative for the contemporary practitioners of Ayurveda to document and publish their observations on the clinical safety of classical herbomineral formulations as such studies will enable the scientific community to believe traditional systems also as evidence based. The current work is an effort to document the clinical safety as well as the off- label indications for Arogyavardhinigutika with objective to review and report dose observations related side-effects and safety of Arogyavardhinigutika.

Key words: Herbomineral, Clinical Safety, Arogyavardhini, Heavy metal

1. INTRODUCTION

Ayurveda bestowed means of positive health and the correct way of living and remedies for elimination of diseases. From the Vedic to Medieval period (2000 BC – 15th C AD there were several changes in the approach of Ayurveda. From 5th Century onwards, the advent of *Rasa Sastra* or the therapeutic processing and use of minerals and metals opened new frontiers for Ayurvedic pharmacology and pharmaco-therapeutics. [1] Though we come across references on the use of calcined lead and iron (*Naga bhasma* and *Loha bhasma*) in the Vedic literature (2000 BC), their utility in therapeutics is limited in the *Brihattrayi* (Charaka samhita, Sushruta samhita and Astanga hrdya). [2,3] Though texts like *Rasa Hridaya Tantra* and *Rasarnava* form the early works on Rasa-Sastra (10-12th C), but later works like *Rasa Ratna Samucchaya* (19th C) are more popular presently. We come across one of the renowned Rasa formulation *Arogyavardhinigutika* in the Rasa Ratna Samucchaya. *Arogyavardhinigutika* is also famous with the names *Arogyavardhinivati* and *Arogyavardhiniras*. *Arogyavardhinigutika* is indicated for skin conditions and finds uses in liver disorders, menstrual disorders etc. *Arogyavardhinigutika* is considered to be one among the top ten classical formulations in the Ayurvedic Formulary of India.[4,5]

Herbomineral formulations such as *Arogyavardhinigutika* are being successfully used in Ayurvedic therapeutics since centuries but there have been reports questioning safety of their metallic contents, especially the presence of heavy metals.[6] The safety of *Arogyavardhinigutika* formulation has been established in preclinical studies where results have suggested that Arogyavardhini vati in the doses equivalent up to 10 times of the human dose administered to rats for 28 days did not have appreciable toxicological effects on brain, liver and kidney. [7] It now becomes imperative for the contemporary practitioners of Ayurveda to document and publish their

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observations on the clinical safety of classical herbomineral formulations as such studies will enable the scientific community to believe traditional systems also as evidence based. The current work is an effort to document the clinical safety as well as the off- label indications for *Arogyavardhinigutika* with objective to review and report dose observations related side-effects and safety of *Arogyavardhinigutika*.

2. MATERIALS & METHODS

2.1 Study Product

Arogyavardhinigutika (Mfd: Dabur India Ltd) was used in the present study. The composition details of Arogyavardhinigutika are given in Table 1.

Table 1: Details of the Arogyavardhini Gutika - Contents*

Contents	Quantity (mg)
Kajjali (Black sulphide of mercury), Amalaki (Emblica officinalis, P.), Haritaki (Terminalia chebula, P.), Bibhitaka (Terminalia belerica, P.)	11.36
Suddha Guggulu (Commiphora wightii, Exd.), Chitraka (Plumbago zeylanica),	22.72
Katuka (Picrorrhiza kurroa)	124.98
Lauh Bhasma, Abhraka Bhasma, Tamra Bhasm (Calcined iron, mica and copper)	17.24
Suddha Shilajatu,	17.04mg
Permitted Excipients: Q.S. Preservatives: Sodium Methyl Paraben I.P.	
*Each tablet of 250mg Ref: (Ra.Ra.Sa. Kushtaroga Chikitsa)	

2.2 Method

Patients attending the various OPDs of Sri Dhanwantry Ayurvedic College and Hospital, Chandigarh during 1st October 2014 to 31st January 2015, formed the subjects of the current study.

The ***Sastry's Safety Score (SSS) Sheet for Heavy Metal Toxicity*** * was used to understand/ assess clinical toxicity of Arogyavardhinigutika in patients consuming this medicine orally for 1-12 months period.[8,9] The patients were followed up for further 1 - 2 months after the completion of treatment. An attempt was also made to review the subject's clinical condition before and after the oral administration of *Arogyavardhinigutika*. On the other hand, their LFT & RFT were obtained wherever possible. The format of SSS sheet is given in Figure 1.

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Figure 1: ***SASTRY'S SAFETY SCORE*** **SHEET FOR HEAVY METAL TOXICITY**

S			***SASTRY'S SAFETY SCORE*** **SHEET FOR HEAVY METAL TOXICITY**											
	Arsenic		**Lead**		**Mercury**		**Iron**		**Copper**		**Tin**			**Zinc**
	Acute		***Acute***		***Acute***		***Acute***		***Acute***		***Acute***			***Acute***
	Fulminanat type:				*First Phase:*									
1	Shock & Peripheral vascular failure	1	Metallic taste	1	ashy colour of mouth	1	Mild GI disturbances	1	burning/pain stomach	1	vomiting and diarrhea		1	vomiting
2	fall in blood pressure	2	diarrhoea	2	bloody diarrhoea	2	abdominal colic	2	Blue/green vomitus	2	skin irritation		2	metallic styptic taste
	GI type:	3	peripheral circulatory failure	3	*Second Phase: 1-3 days*	*3*	Nausea	3	Severe headache	3	central nervous system		3	dyspnoea
3	like bacterial food poisoning	4	insomnia	4	Renal Failure	4	vomiting	4	Oliguria / Hematuria	4	cramps		4	hemorrhagic nephritis
4	smell of garlic in breath & stool	5	depression / coma	5	Colitis	5	diahhroea	5	Convulsions / spasm	5	muscle pain		5	tetanic spasms
	Other findings:													
5	skin eruptions / pigmentation													
	Chronic		***Chronic***		***Chronic***		***Chronic***		***Chronic***		***Chronic***			***Chronic***
1	Polyneuritis, paraesthesia etc	1	Blue line on gums (Burtonian line)	1	Fine Generalized Tremors	1	hemochromatosis	1	Green line on gums	1	benign pneumoconiosis		1	Dyspepsia
2	Skin bronzing / alopecia	2	Wrist drop etc. (Lead Palsy)	2	Gingivitis / Salivation	2		2	Anaemia / hemolysis	2	dermatitis		2	Colic & constipation
3	Chronic Nephritis	3	Chronic nephritis	3	Renal Failure	3		3	Renal Failure	3	Renal Failure		3	Diarrhoea
4	Liver Cirrhosis	4	Anaemia (poikilocytosis)	4	Mercurial Erethism	4		4	Diarrhoea & maliase	4	Skin pigmentation (rarely)		4	Anemia
5	Anaemia & weight loss	5	Emaciation	5	Malt-Brown reflex	5		5	Atrophy of muscles	5	stannosis		5	Peripheral neuritis
SCORING:		**SCORING:**		**SCORING:**		**SCORING:**		**SCORING:**		**SCORING:**			**SCORING:**	
0	Safe	0	Safe	0	Safe	0	Safe	0	Safe	0	Safe		0	Safe
1	Mid	1	Mid	1	Mid	1	Mid	1	Mid	1	Mid		1	Mid
2	Moderate	2	Moderate	2	Moderate	2	Moderate	2	Moderate	2	Moderate		2	Moderate
3	Severe	3	Severe	3	Severe	3	Severe	3	Severe	3	Severe		3	Severe

Statistical Analysis: All statistical comparisons were made using repeated measures ANOVA

*Sastry's Safety Score (SSS) Sheet for Heavy Metal Toxicity" has been developed by Sastry & Prasad, (2006) to assess clinical safety/ toxicity of herbomineral formulations containing heavy metals. In SSS sheet, the evaluation was made basis the five (5) fulminant, subacute and chronic toxicity symptoms of seven (7) heavy metals used in herbomineral formulations viz.; arsenic, lead, mercury, iron, copper, tin and zinc have been identified and assessed on a 4 point scale where 0=safe, 1=mild, 2=moderate and 3=severe. The format also assess whether any of the heavy metal toxicity related symptoms are visible in subjects consuming herbomineral preparations.

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3. RESULTS AND DISCUSSION

3.1 Demographic Details

The subjects in the present study were of either sex between the age ranges of 16-84 years. The mean age of the subjects (n=809) was 34.26 yrs (+ 14.87). Out them, there were 697 female subjects (86.16%) and 112 male subjects (13.84%). The mean age of females was 30.93 yrs (+ 21.08 yrs) and the mean age of males was 37.51 yrs (+ 23.42 yrs). All the subjects were assessed as per their ailments and the details are given in Table 2.

Table 2: Arogyavardhinigutika - Indications

Indications		
Aadhman	Jvara	Vibandha
Abhisyand	Amalpitta	Striroga/ Garbhashayagata roga
Agni mandya	Pratishaya	Arbud
Ajirna	Twak vikaar	Atisara
Allergy	Udarshoola	Bandhyatava
Amalpitta	Yakritvikar	Medoroga
Amavata	Vatvyadhi	Nasagata roga
Anaah	Artava vikar	Pradar- Shweta/ Rakta
Anidra	Pandu/ kamala	Garbhashayamukha vrana
Epiphora	Garbhashya arbuda	
Grahani	Granthi	

3.2 Dosage Pattern

The minimum and maximum doses of each of the medicines used in this study were assessed to understand the dose related toxicity levels. The 809 patients (n=809) received *Arogyavardhinigutika* at a dose of 500 mg to 1500 mg per day either as stand alone or as combination therapy for specified disease conditions. The minimum period of oral consumption was 1 month while the maximum was 6 months. The dosage pattern was tabulated (Table 3).

Table 3: Ingredient Quantity* *vs* Recommended Doasge and Toxic Dosage in Arogyavardhini Gutika

S. No	Ingredient	Qnty as per text	Qty in 250 mg	Qty in 300 mg	Qty in 450 mg	Allowed	Fatal Dose
1	Parada (Suddha)	1 part or 10 g	6.94 mg	8.33 mg	12.5 mg	30-120 mg	1 to 4 g
2	Gandhaka (Suddha)	1 part or 10 g	6.94 mg	8.33 mg	12.5 mg	120-960 mg	--
3	Loha Bhasma	1 part or 10 g	6.94 mg	8.33 mg	12.5 mg	30-240 mg	2 to 4 g
4	Abhraka Bhasma	1 part or 10 g	6.94 mg	8.33 mg	12.5 mg	120-240 mg	--
5	Tamra Bhasma	1 part or 10 g	6.94 mg	8.33 mg	12.5 mg	15-60 mg	30 g / 15 g
6	Triphala Churna	2 parts or 20 g	13.88 mg	16.67 mg	25 mg	--	--
7	Shilajit (Suddha)	3 parts or 30 g	20.83 mg	25 mg	37.5 mg	--	--
8	Guggulu (Suddha)	4 parts or 40 g	27.77 mg	33.33 mg	50 mg	--	--

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9	Chitramula	4 parts or 40 g	27.77 mg	33.33 mg	50 mg	--	--
10	Katuki	180 parts or 180 g	125 mg	150 mg	225 mg	--	--
* Each 250 mg Tablet							

On the basis of above information, the safety of Ayurvedic bhasma ingredients with special reference to modern toxicological descriptions was also evaluated. The reference values are given in Table 4. [10-13]

Table 4: Fatal Dose and Fatal Times of Heavy Metals

Parameter	Arsenic	Lead	Mercury	Iron	Copper	Tin	Zinc
FATAL DOSES	oxides 200 mg	acetate 20 mg	1 to 4 g	>300 mg	Sulphate 30 g	10-20 mg	sulphate 15 g
		carbonate 30 mg			subacetate15g		chloride 1-4 g
							phosphide 0.5-1 g
FATAL TIME	1- 2 days	1 to 2 days	few hrs to 1-2 wks	few months	1 to 3 days		few hrs to days
Toxicity Status as Metal	non-toxic	toxic	Toxic	toxic	non-toxic	toxic	toxic

Assessment was also made in comparison with individual bhasma dosage and modern toxic / fatal doses versus metallic / mineral ingredient in a particular formulation. The cumulative effect or toxicity with poly metallic or poly mineral ingredient was also carefully evaluated.

In *Arogyavardhinigutika*, dosage of metallic ingredients was less than the recommended and fatal doses. The minimum and maximum of *Parada* (mercury), *Loha* (iron) and *Tamra* (copper) bhasmas were 13.88 mg and 37.5 mg each per day.

It was also observed that the therapeutic doses recommended / allowed in Ayurvedic texts for individual bhasmas *vis a vis* the doses of the metallic ingredients within a given formulation were not the same. In fact, the latter were found to be less in quantity compared to individual bhasma dosage forms. Similarly, the recommended doses in the Ayurvedic literature are far below compared to the toxic / fatal doses mentioned in modern toxicology texts. A careful clinical examination is done for evaluation of these subjects but did not reveal any serious adverse effect.

3.3 RFT & LFT values

Among these subjects (n=809) there were 86 subjects for whom the renal functional tests and liver function test reports were available at the baseline and during the course of treatment / end of study. These results were obtained from the laboratory records for random assessment.

RFT values: The mean S. Creatinine in about 86 patients (randomly picked from non-renal cause group) of this study was 1.43 mg/dl (± 0.02 mg/dl) at the baseline and was 1.41 mg/dl (± 0.031 mg/dl) at the end of therapy. This is found to be statistically not significant (p=<0.001) on application of repeated ANOVA. The mean S. Urea in these 207 patients was 39.44 mg/dl (± 2.12 mg/dl) at the baseline and it was about 40.21 mg/dl (2.09 mg/dl) at the end of therapy. This is found to be statistically not significant (p=<0.001) on application of repeated ANOVA.

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S. Creatinine in the renal cause group (n=23) receiving *Arogyavardhinigutika* was about 1.67 mg/dl at the baseline and was found to be 1.65 mg/dl at the end of the study. This is found to be statistically not significant (p=< 0.001) on application of repeated ANOVA.

LFT values: It was also observed that the SGPT (ALT) and SGOT (ALS) were 34.25 mg/dl and 41.23 mg/dl at the baseline respectively. There was no significant change in their mean readings at the end of the study viz., 36.26 mg/dl and 40.98 mg/dl for SGPT and SGOT respectively. There is no change in the S. Bilirubin (total) of these patients (non-jaundice group). These are found to be statistically not significant (p=< 0.001) on application of repeated ANOVA.

The final results are suggestive that none of the patients (who received the above formulations for 3-12 months) have shown any signs of toxicity as evaluated against the symptoms mentioned in toxicology texts. Neither, their blood samples give any evidence of hepatic or renal damage. This supports the hypothesis that the Ayurvedic metal-mineral and herbo-mineral formulations act as hydrophobic / lyophobic colloids and chelates / ligands respectively. Therefore, they are safe in general and the same is to be monitored on the basis of dosage patterns.

On the application of repeated measure ANOVA there is no significant variation in the toxicity level on the basis of Sastry's Score Sheet between the monthly intervals starting from first month to twelfth month (p = < 0.001).

The Ayurvedic texts mention that a poison may be used as best medicine or *vice versa* is also possible if it is used indiscriminately (C.S.Su.1). Lead (Naga) and tin (Vanga) are actually indicated for Prameha when properly manufactured. If improperly made, they are said to cause Prameha as side effect. This shows that the ancient physicians of Ayurveda possessed thorough knowledge on safety profiles of *Arogyavardhinigutika*.

4. CONCLUSION

Conventionally, modern toxicology and pharmacology consider the salts of heavy metals are highly toxic considering their specific gravity. Interestingly, the metals like mercury and copper are found to be non-toxic while their salts are highly toxic. The study affirms that the Ayurvedic Herbomineral formulation Arogyavardhini Gutika when conventionally prescribed in Ayurveda as safe basis absence of serious adverse reactions or toxicity symptoms. The results may also indicate that the Ayurvedic metallo-mineral and herbo-mineral formulations may safe if carefully administered. This study is an attempt to debate the conventional thinking of modern science / medicine that there may be cumulative effect of poisoning with Ayurvedic herbomineral formulations comprising heavy metals.

It may also be borne in mind that atomic absorption spectroscopy may not detect the ligand / chelate chain attached to the Ayurvedic bhasmas and alternative methods of analysis need be developed. The authors intend to further continue with the study of other classical formulations also on the same lines to establish the safety studies. The Ayurvedic mineral or herbo-mineral drugs should be studied for ligands, nano-particles and colloids. The Ayurvedic bhasmas are to be studied for chelates as well.

This study proves the importance of observational studies and research as basis for EVIDENCE BASED AYURVEDA. Finally, it is to be concluded that - ***IT IS THE 'CLINICAL SAFETY', BUT NOT THE LABORATORY TOXICITY WHICH COUNTS IN THE END***.

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