Research Article

Safety of Mahayogaraj Guggulu (A Herbo Mineral Formulation): an Observational Study

Tripathi S[1], Pandey S D[1], Sastry J L N*[2], Sasibhushan V[2]
1. Shri Dhanwantry Ayurvedic College, Sector 46B, Chandigarh, India.
2. Dabur Research & Development Centre, Sahibabd, Ghaziabad Dist., Uttar Pradesh, India.
***Corresponding author's E-mail:** j.sastry@mail.dabur

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ABSTRACT

Herbomineral formulations such as Mahayograj Guggulu 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. 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 observational study in an effort to document the clinical safety of Mahayograj Guggulu with objective to review and report dose observations related side-effects and safety of Mahayograj Guggulu.

Keywords: Mahayograj Guggulu herbomineral, heavy metal, clinical, safety.

INTRODUCTION

Existence of Ayurveda is believed to be pre historic due to fundamental concept of *Panch Mahabhut*. Ayurveda has identified and incorporated all the naturals as medicine having their eternal potency due to value added properties like *Haritaki, Bibhitaki, Amalaki, Guduchi* etc., *Guggulu* is one such natural drug which is considered as *Divyaaushadi* by ancient sages/ancestors who were the earliest practitioners of Ayurveda.

Guggulu, the oleo gum resin secreted by *Commiphora mukul*, has been used widely in Ayurvedic formulations. *C. mukul* is a short thorny shrub that is native to the Indian subcontinent. Oleo gum resin extracted by incision of the bark is a very complex mixture of gum, minerals, essential oils, terpenes, sterols, ferrulates, flavanones and sterones. Its active constituents, the Z- and E-guggulsterones, have been demonstrated to exhibit their biological activities by binding to nuclear receptors and modulating the expression of proteins involved in carcinogenic activities. Guggulsterones have also been reported to regulate gene expression by exhibiting control over other molecular targets including transcription factors such as nuclear factor (NF)-κB, signal transducer and activator of transcription (STAT) and steroid receptors. Considerable scientific evidence indicates the use of gum guggulu as a therapeutic agent in the treatment of inflammation, nervous disorders, hyperlipidaemia and associated cardiac disorders such as hypertension and ischaemia, skin disorders, cancer and urinary disorders.[1-24]

Mahayogaraj guggulu (MYG) is a widely used Ayurvedic formulation. MYG is one among those Ayurvedic formulations listed by Saper[3-4] as having an unacceptably huge metallic content. MYG has been in use in Ayurveda for the treatment of various neurological disorders.[5] As a general rule in Ayurvedic therapeutics, Guggulu is administered in combination with other herbs. Some of the Guggulu containing Ayurvedic formulations include *Triphala guggulu, Yogaraj, Mahayogaraj guggulu, Chandraprabha vati, Simhanada guggulu, Gokshuradi guggulu, Kanchanara guggulu, Amritadi guggulu, Lakshadi guggulu, Kaishora guggulu, Navaka Guggulu* etc. These Guggulu preparations are used commonly for diseases of musculoskeletal systems and also for hyperlipidemia.[5-9]

Herbomineral formulations such as MYG 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. 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 was an effort to document the safety as well as the off- label indications for MYG with objective to review and report dose observations related side-effects and safety of MYG.[10-14]

MATERIALS AND METHODS

Study product

Maha Yogaraj Guggulu manufactured by Dabur India Ltd was the study drug for this study. The composition details of MGY are given in Table 1.

Methods

Patients coming for the consultation to different OPDs of Sri Dhanwantry Ayurvedic College & Hospital, Chandigarh between 1st October 2014 to 31st January 2015, have

formed the subjects of the present study. Ethical committee clearance was not taken as in this study, the data was considered from the hospital software to survey the prescription patterns in the regular OPD and also to report any untoward effects of MYG. The dose related side-effects/safety of MYG were reviewed and the observations have been reported.

"***Sastry's Safety Score (SSS) Sheet for Heavy Metal Toxicity***" was used to understand clinical toxicity of MYG in patients consuming this medicine orally for 01-04 months period. The follow up period was also 1-2 months after the completion of treatment. The evaluation was made on 5 symptoms or conditions (in acute and chronic toxicity categories). Acute and chronic toxicity symptoms are graded as safe, mild, moderate and severe on a 4 point scale where 0=safe, 1=mild, 2=moderate and 3=severe. An attempt is made to review the subject's clinical condition before and after the oral administration of MYG. A format was made to assess the patients whether any of the heavy metal toxicity.

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. Related symptoms (acute or chronic) are visible on the subjects or not (Fig.1). On the other hand, their LFT & RFT are also obtained where ever possible. Statistical evaluation was carried out using repeated measure ANOVA at 5% significance level.[15-18]

Table 1: Details of the Dabur Yograja Guggulu (Maha) Contents[7]*

Contents	Quantity (mg)
Shunthi (Zingiber officinale, Rz.), Pippali (Piper longum, Fr.), Chavya (Piper retrofractum, St.), Pippalimula (Piper longum, Rt.), Chitraka (Plumbago zeylanica, Rt.), Suddha Hingu (Ferula foetida, Exd.), Ajamoda (Apium leptophyllum, Fr.), Sarshapa (Brassica campestris, Sd.), Shvetajiraka (Cuminum cyminum, Fr.), Krishnajiraka (Carum carvi, Fr.), Renuka (Vitex negundo, Fr.), Indrayava (Holarrhena antidysenterica, Sd.), Patha (Cissampelos pareira, Rt.), Vidanga (Embelia ribes, Fr.), Gajapippali (Scindapsus officinalis, Fr.), Katuka (Picrorhiza kurroa, Rz.), Ativisha (Aconitum heterophyllum, Rt. Tr.), Bharangi (Clerodendrum serratum, Rt.), Vacha (Acorus calamus, Rz.), Murva (Marsdenia tenacissima, Rt.)	1.07 *each*
Amalaki (Emblica officinalis, P.), Haritaki (Terminalia chebula, P.), Bibhitaka (Terminalia belerica, P.)	14.36
Suddha Guggulu (Commiphora wightii, Exd.)	64.65
Vanga Bhasma, Rajat Bhasma, Naga Bhasma, Lauh Bhasma, Abhraka Bhasma, Mandura Bhasma, Ras Sindura	17.24
Permitted Excipients: Q.S. Preservatives: Sodium Methyl Paraben I.P.	
*Each tablet of 250mg	

Table 2: Dose of Bhasmas considered as Heavy metals as Per AFI

S. No	Name of the Bhasma	Quantity of Bhasma As per AFI
1	Loha Bhasma	120 mg to 250 mg
2	Rasa Sindhura	125 mg
3	Vanga Bhasma	125 mg to 250 mg
4	Naga Bhasma	62.5 mg to 125 mg

Table 3: Fatal Dose and Fatal Times of Heavy Metals

	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

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

OBSERVATIONS AND RESULTS

This observational study included 163 subjects who were suffering with musculoskeletal related diseases. They were between the age group of 16-84 years and belong to both the sex. The mean age of the subjects (n=163) was 49.54 years, out them there were 105 female subjects (64.41%) and 56 were male subjects (34.35%).

It was observed that MYG is orally administered / prescribed at a dose of 250 mg twice daily to 500 mg twice daily.

Observations in current study show that subjects received MYG at a dose of 500 mg to 1000 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 4 months. The minimum and maximum doses of Maha Yograj Guggulu used in this study were assessed for any metal toxicity (acute and chronic) using Sastry safety score sheet to understand the dose related toxicity levels.

Ayurvedic bhasma ingredients with special reference to modern toxicological descriptions was also evaluated. The reference values are indicated below.Assessment was also made in comparison with individual bhasma dosage and modern toxic/fatal doses versus metallic/mineral ingredient in a particular formulation.[19-20]

It was observed that in MYG, dosage of metallic ingredients was less than the recommended and fatal doses. The minimum and maximum administration of *Loha* (iron) bhasma, Rasa Sindhura (Mercury), Naga (Lead) bhasma and Vanga (Tin) bhasma in the MYG was 34.48 mg (considering 250 mg of MYG twice daily) to 68.96 mg (Considering 500 mg of MYG twice daily) each per day.[21-22]

It is 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 are not the same. In fact the later are found to be less in quantity compared to individual bhasma dosage forms (Table 2). Similarly, the recommended doses in the Ayurvedic literature are far below compared to the toxic/fatal doses mentioned in modern toxicology texts(Table 3).[15-16] A careful clinical examination is done for evaluation of these subjects but did not reveal any serious adverse effect.

RFT & LFT values

Among these subjects (n=163) there were 86 subjects for whom the renal functional tests & 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 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 36 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.

S. Creatinine in the (n=86) receiving *Chandraprabhavati* 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) & 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 & SGOT respectively. There is no change in the S. Bilirubin (total) of these patients. These are found to be statistically not significant (p=< 0.001) on application of repeated ANOVA.

The final observations are suggestive that none of the subjects (n=163) who received MYG for 1-4 months has 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. 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 fourth month (p = < 0.001).

DISCUSSION

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). The formulations prepared as per text will have a distinct edge over improperly made. Formulations prepared without proper shodana and not following the SOP may cause diseases like Prameha (Diabetes), Skin diseases as side effect. Though the relative safety of MYG has been established in preclinical studies, the current study shows that the ancient physicians of Ayurveda were possessing thorough knowledge on safety profiles of MYG. Bhasmas, which are unique Ayurvedic metallic/mineral preparations are biologically produced nanoparticles (NPs) prescribed with several other medicines of ayurveda[5].

The authors intend to further continue with the study to observe the safety in more number of subjects for a period of one year. The Ayurvedic mineral or herbo-mineral drugs should be studied or tested for ligands, nano-particles and colloids but not for metal quantity.

The conventional parameters used to analyze the mineral and herbo mineral products will not sufficient for these kinds of formulations as they use destructive methods to analyze the metals. Rasaoushadis are not merely metallic salts of concerned metals but they are organic compounds where metals are transformed into a state of colloids

CONCLUSION

Non availability of serious adverse reactions or toxicity symptoms MYG proves that the Ayurvedic metallo-mineral and herbo-mineral formulations are safe if carefully administered. This study also disproves the conventional thinking of modern science/medicine that there will be cumulative effect of poisoning with these Ayurvedic formulations.

As destructive methods of analysis (like AAS) can't detect the ligand/chelate chain attached to the Ayurvedic bhasmas alternative methods of analysis to be developed.

This study proves the importance of observational studies and research as basis for EVIDENCE BASED AYURVEDA. Clinical safety should be given first than the analytical limits and parameters.

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