Review Article

Efficacy of Makaradhwaja on Madhumeha (Type2 Diabetes) – A Review through Ayurvedic Studies

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ABSTRACT

Makaradhwaja is a herbo-metalo-mineral formulation mainly composed of gold, mercury and sulphur. It is a renowned rejuvenating, immuno-modulator and aphrodisiac formulation being used in many disorders viz. asthma, Koch's disease, hyperpyrexia and diabetes mellitus (DM). DM is a rising threat to global health as it involves multisystem pathologies, complex metabolic aberrations and varied clinical manifestations. Among all available studies on *Makaradhwaja* only three clinical and experimental works has been found conducted till date proving its efficacy on *Madhumeha*. Present study has been planned to compile these studies to revalidate the efficacy of *Makaradhwaja* in DM. Both TBM (*Makaradhwaja* prepared by processing the mercury with three times sulphur) and SBM (*Makaradhwaja* prepared by processing the mercury with six times sulphur) showed promising results in treatment of DM, where SBM shown comparatively better results.

Keywords: *Makaradhwaja*, Diabetes mellitus, *Rasayana*, *Kupipakwa*, *Bhasma*, *Madhumeha*.

INTRODUCTION

Makaradhwaja is one of the most popular *Rasaushadhi* (herbo-metalo-mineral compound formulations) prepared with *Shodhita* (processed) *Swarna* (gold), *Shodhita Parada* (mercury), and *Gandhaka* (sulphur) by *Kupipakwa* method (gradual heating process in glass bottle) of preparation using *Valuka Yantra* in the ratio of 1:8:16,[1] 1:8:24[2] or 1:8:48.[3] It is well known aphrodisiac,[4] immuno-modulator,[5,6] rejuvenator[7] drug being used in many ailments viz. *Shwasa* (asthma), *Kshaya* (Koch's disease), *Jwara* (hyperpyrexia) and *Madhumeha* (diabetes).[8,9] In context of *Makaradhwaja* different formulations are found and these are found different just due to varying in the proportion of *Gandhaka* with *Parada.* Some text quoted that proportion of *Gandhaka* is twice, thrice or six times of *Parada*. By adopting these

methods TM and SM are prepared in Ayurvedic pharmaceutical industries.

Diabetes mellitus (DM) is emerging threat to public health due to its multisystem involvement, complex metabolic abnormalities, multiple clinical manifestations and remote complications. It is commonly manifested as elevation in blood glucose levels (hyperglycemia), resulting from either a defect in insulin secretion from the pancreas, insulin resistance in cells or both.[10] The global burden due to diabetes is mostly contributed by type 2 diabetes which constitutes 80% to 95% and in India it constitutes almost 98% of the total diabetic population. Presently 61.3 million people are suffering from DM in India which could reach 101.2 million by 2030.[11] In Ayurveda, type 2 DM is correlated with *Madhumeha* which is *Tridosha* dominant disease.[12-14]

Several research works have been carried out on *Makaradhwaja* in various Ayurvedic institutes all over India;[15-17] of them, only three are conducted on with special reference to *Madhumeha*. The present attempt is to review these studies and revalidate the therapeutic efficacy of *Makaradhwaja* on *Madhumeha*.

MATERIALS AND METHODS

All the relevant studies carried out all over the country as well as the available published papers in electronic databases (various databases viz. PubMed, ScopeMed, PubMed Central Databases, DHARA online database and other allied databases) are thoroughly reviewed. Ayurvedic literature is also screened and critically analyzed. Only three research works are found to be carried out to prove clinical efficacy of *Makaradhwaja* on *Madhumeha* at PG and PhD levels upto 2014 in Jamnagar. *Makaradhwaja* were prepared by different ratio of *Gandhaka* known as *Balijarana*, as it is claimed in context of *Makaradhwaja* that increase in the *Balijarana* augment the therapeutic potency.[18,19]

Criteria for selection of patients

Inclusion, exclusion, diagnostic and assessment criteria of patients in all studies were same except age group whose lower limit was varied from 20-35 years and upper limit from 70-75 years. Patients having classical symptomatology of *Madhumeha*[20] have been selected from the out-patient and in-patient departments of IPGT and RA, Gujarat Ayurved University, Jamnagar, India. Patients having age group between 20 to 75 years was selected with no bar of race, sex, or religion. Patients were included having fasting blood sugar level ≥ 126 mg/dl or 2 hr plasma glucose level ≥ 200 mg/dl and up to 600 mg/dl.[21] Several investigations were carried out on glycemic levels, liver function test, renal function test and lipid profile to diagnose and rule out any other associated pathological condition. All studies were carried out after obtaining permission from institutional ethical committee. Written Informed Consent was also taken from patients as per declaration of Helsinki after providing sufficient information regarding the study and its aim.

Exclusion criteria

Patients having insulin-dependent DM or chronic complications of DM; such as microvascular (Retinopathy, Neuropathy and Nephropathy)/macrovascular (coronary artery disease, peripheral artery disease etc), Tuberculosis, AIDS, and malignancies.

Clinical trial 1

MKP [*Makaradhwaja* prepared with *Swarna Patra* (thin sheets of gold)], MKV [*Makaradhwaja* prepared with *Swarna Varkha* (gold foils)] and MKB [*Makaradhwaja* prepared with *Swarna Bhasma* (incinerated ash)] were prepared by using *Hingulottha Parada* (mercury

extracted from cinnabar) in the ratio of 1:8:24, in accordance with the reference of *Bhaishajya Ratnavali*.[22] Drugs were administered in capsules containing 125 mg of TM and 125 mg of *Guduchi Ghana* (GG) (aqueous extract of *Tinospora cordifolia*), 15 minutes before meal, with honey, for 28 days. GG was prepared as per reference of *Siddha yoga sangraha.*[23] GG was also administered at a dosage of 250 mg BD in capsule form in control group. Total 140 patients were registered for the study and randomly divided into 4 groups as shown in Table 1.[24,25]

Clinical trial 2

The study was designed to establish the efficacy of *Triguna Makaradhwaja* (*Makaradhwaja* prepared by processing the mercury with three times sulphur) (TBM) and *Shadguna Makaradhwaja* (*Makaradhwaja* prepared by processing the mercury with six times sulphur) (SBM) prepared with *Ashtasamskarita Parada* (octa-processes to purify and potentiate mercury)[26,27] in *Madhumeha*. Capsules of TBM and SBM were administered (250 mg each), containing 17.5 mg of respective drug and 232.5 mg of GG.[23,28,29] GG was administered (250 mg capsule) as control group. The drugs were administered twice a day, half hour before meal, with honey, for 28 days. Total 153 patients were registered and randomly allocated into 3 groups (Table 1).[30]

Clinical trial 3

Triguna Balijarita Makaradhwaja (TBM*)* with *Shodhita Swarna, Hinguloattha Parada,* and *Shodhita Gandhaka* (1:8:24)[22] and *Shadguna Balijarita Makaradhwaja* (SBM) prepared as per classical reference (1:8:48). A tablet of TBM and SBM of 250 mg containing 14.63 mg of respective drugs and 235.37 mg of GG[23,28,29] was administered twice a day, half an hour before meal, with honey, for 28 days. Double blind clinical trial was conducted on 73 patients, randomly allocated in two groups TBM and SBM (Table 1).[31]

Criteria for assessment

The results of the therapy were assessed after completion of treatment on the basis of improvement in the signs and symptoms based on both Ayurvedic and modern parameters and investigations conducted before and after treatment. For the assessment of the effect of the therapy following chief complaints and biochemical parameters were selected-*Prabhutamutrata* (polyuria), *Avilamutrata* (urine turbidity), *Trishnadhikyata* (polydypsia), *Klaibyata* (loss of libido), *Karapadasuptata* (numbness over hands and feet), *Daurbalyata* (weakness), *Pindikodweshtana* (calf muscle cramps), *Shramapratiti* (exhaustion), *Kshudhadhikyata* (polyphagia), *Karapadataladaha* (burning sensation over palms and soles), Fasting blood sugar, Post-prandial blood sugar, SGOT, SGPT, S. cholesterol, S. triglycerides, S. HDL, S.VLDL, S. LDL, S. Calcium, Direct and indirect bilirubin, S. Protein and alkaline phosphatase, S. Urea, S Creatinine.

Statistical analysis

The obtained data was analyzed statistically using paired and unpaired ‘t’test, one way ANOVA and Dunnet’s t test, here the level of significance was taken as $P<0.05$, $P<0.01$ and $P<0.001$ were considered as statistical significant and highly significant respectively.

Pharmacological studies of *Makaradhwaja* on diabetes

Antidiabetic activity was conducted in all three clinical trials using steptozotacin induced diabetic animals (albino wistar rats). These studies were carried out after

obtaining permission from Institutional Animal Ethics Committee.[32,33]

RESULTS AND DISCUSSION

Ayurveda has also given utmost importance towards quality of drug, standard preparation methods, and their mode of usage comprehensively.[34-36] All these three studies were randomized; among them, two were open label and one was double blind study. Total 375 patients are included in these studies. No allopathic drug was administered along with *Makaradhwaja* in these clinical trials.

In clinical trial 1, there was statistically highly significant reduction in signs and symptoms in all of 3 test groups, where MKB group showed comparatively better result in overall effect of therapy among test drugs (figure 1). Here control group (GG) exhibited significant relief only in three symptoms viz. *Trishnadhikya, Kara-Pada-Tala Daha, Kara-Pada Suptata*, and non significant relief in others. This nullifies the chance of highly significant reduction in signs and symptoms of disease in all three test drugs due to GG. MKV was found comparatively effective in controlling glycemic levels, while MKB was found effective in relieving signs and symptoms. FBS and PPBS was found reduced in all test drug groups, whereas it was increased in GG group, which further denies possibility of reduction of blood sugar merely due to GG as shown in table 2.[24]

In clinical trial 2, SBM group showed statistically highly significant reduction in all signs and symptoms. TBM and GG groups also showed statistically highly significant reduction in all symptoms except *Pindikodweshtana* and *Klaibya*. Overall, SBM showed comparatively better results in subjective as well as objective parameters (figure 1) (table 2).[30]

In clinical trial 3, SBM was found more effective than TBM in view of total effect of therapy (figure 1). There was comparatively more reduction in FBS and PPBS in SBM group than TBM group. There was comparatively more reduction in observed signs and symptoms in SBM than TBM group except *Pindikodweshtana*, in which there was statistically highly significant reduction in both the groups**.** This implies anti-hyperglycemic effect of *Makaradhwaja*.[32] Highly significant decrease was observed in blood urea level in SBM whereas non-significant mild decrease was observed in TBM. Breakdown of proteins results in the formation of ammonia which is very toxic and is immediately converted in to urea in liver and excreted through kidney in the form of urea. The decrease in blood urea level denotes decreased catabolism of proteins (which means increased glucose uptake for energy production which is very much helpful for the diabetic patients). It also implies increased functioning ability of liver as well as kidney after therapy as shown in Table 2.[31]

As there were differences in pharmaceutical processing as well as administered doses of formulations, hence it is difficult to firmly conclude comparative statement of efficacy of all formulations collectively on disease as whole. Clinically maximum anti-diabetic effect was found in MKV than by MKB and MKP. SBM showed better therapeutic efficacy than TBM and GG. This ultimately proves, more the number of processing done with *Gandhaka*, more effective will be *Makaradhwaja.* Many experimental studies carried out to establish the safety and efficacy of drug. [37,38]

Animal experimentation was also conducted in these clinical trials to ascertain the antidiabetic activity. All studies showed moderate to good anti-diabetic activity on streptozotacin induced diabetes in experimental animals. Diabetes induced

fatty changes in renal tissue were also attenuated with *Makaradhwaja*. The experimental effect may be ascribed to regeneration of beta cells of pancreas.[24,30-33]

In all aforesaid studies, *Makaradhwaja* was administered along with GG as adjuvant, having *Rasayana* property, which helps in rejuvenating the *Dhatus* (seven basic tissues) and helps to break the *Tridoshaja* pathogenesis of *Madhumeha*.[39,40] *Guduchi* is well known antihyperglycemic, antioxidant, immunomodulator, rejunavator drug.[41-43] In Ayurvedic classics, *Madhu* (honey) is advocated to be used as anti-diabetic, especially in many herbo-mineral formulations (e.g. *Makaradhwaja*) as a vehicle drug, which is also validated by current evidences.[44,45] Structurally *Makaradhwaja* is detected as mercuric sulphide (HgS), which is found to be pharmacologically safe. Sulphides of Mercury are well absorbed in stomach in the presence of gastric juice in very minute quantity. But there is no any evidence of mercury was found as traces in the body fluids after absorption of these Sulphides. It means only Sulphide contents are absorbed in stomach and not Mercury, which is excreted with faeces[46-50] It is assumed that, Likewise the action of Sulfonylureas group of oral hypoglycemic agents, *Makaradhwaja*, in which Sulfur processed by Mercury and Gold may stimulate the beta cells of pancreas which in turn stimulates the secretion of insulin and thus controls the blood sugar in DM.

No adverse effect of *Makaradhwaja* was reported in any of these trials hence all studies validate the potential of *Makaradhwaja* in treatment of diabetes. Though limitation was observed in these researches the result can be considered as a lead for future studies.

CONCLUSION

All treatment groups showed highly promising results to counter the complex pathology of type 2 diabetes and demonstrated statistically highly significant improvement in subjective as well as objective parameters of *Madhumeha*, where SBM group proved to be more effective than all other groups. Present review also validates the Ayurvedic claims that *Parada* treated with *Gandhaka Jarana* process becomes highly potentiated and the formulation prepared from them possess wide therapeutic utilities.

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Conflict of Interest

None.

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Table 1. Drug, dose and registered patient wise distribution of the respective groups

Trials	Group	Dosage form	Drug	Dose (mg)	Patients Registered		
					Completed	Dropped out	Total
Trial 1	A	Capsule	MKP + GG	125 + 125	30	06	140
	B		MKV + GG	125 + 125	30	08	
	C		MKB + GG	125 + 125	30	04	
	D		GG	250	23	09	
Trial 2	A	Capsule	TBM + GG	17.5 + 232.5	48	04	162
	B		SBM + GG	17.5 + 232.5	52	03	
	C		GG	250	53	02	
Trial 3	H	Tablet	TBM + GG	14.63+235.37	35	01	73
	R		SBM + GG	14.63+235.37	35	02	

MKP- *Makaradhwaja* prepared by *Swarna Patra*; MKV- *Makaradhwaja* prepared by Swarna Varkha, MKB- *Makaradhwaja* prepared by Swarna bhasma; GG – *Guduchi Ghana*.

Table 2. Effect of Makaradhwaja (% relief) on signs, symptoms and biochemical parameters

Parameters/ Groups		Trial 1				Trial 2			Trial 3	
		A	B	C	D	A	B	C	H	R
SUBJECTIVE	*Prabhuta Mutrata*	38.29** ↓	63.46** ↓	60.83**↓	19.51* ↓	51.11** ↓	61.79** ↓	41.18* ↓	58.33**↓	58.73** ↓
	Avila Mutrata	90.32 **↓	83.33** ↓	78.05**↓	22.22* ↓	46.15** ↓	56.99** ↓	37.35* ↓	64.41**↓	71.79** ↓
	Kshudhadhikya	86.95** ↓	85.71** ↓	70.42 **↓	35.14 *↓	57.45** ↓	57.14** ↓	35.63* ↓	71.05**↓	89.19** ↓
	Trishnadhikya	86.66** ↓	80.55** ↓	87.5** ↓	37.03** ↓	40.22** ↓	50.54** ↓	23.46* ↓	71.05**↓	85.29** ↓
	Kara-Pada-Tala Daha	100**↓	91.89** ↓	83.78**↓	33.33** ↓	43.48** ↓	56.52** ↓	29.76* ↓	75.00**↓	85.29** ↓
	Kara-Pada Suptata	86.95** ↓	85.71** ↓	87.09**↓	44.83** ↓	38.46** ↓	54.74** ↓	27.06* ↓	62.50↓	81.82↓
	Daurbalya	81.25** ↓	76.47** ↓	73.07**↓	21.43 ↓	45.56** ↓	56.52** ↓	35** ↓	50.00**↓	70.37** ↓
	Pindikodweshta—na	84.00** ↓	85.18** ↓	75.00**↓	07.14 ↑	NSD	88.42** ↓	NSD	67.50**↓	64.71** ↓
	Klaibya	78.94** ↓	82.34** ↓	83.33**↓	21.05 ↑	NSD	65.24*↓	NSD	18.03*↓	11.42*↓
OBJECTIVE	FBS	12.22↓	18.89** ↓	15.13*↓	09.43↑	10.13*↓	19.14** ↓	18.03* ↓	11.42*↓	12.83** ↓
	PPBS	12.35*↓	18.40** ↓	15.60**↓	02.80↑	15.58*↓	25.46** ↓	29.05* ↓	10.43↓	15.74** ↓
	S. cholesterol	02.56↓	04.10↓	03.48↑	02.63↓	3.07↓	6.08*↓	6.32*	03.93 ↓	04.58↓
	S. Triglyceride	09.27↓	08.43↑	02.05↓	02.91↑	5.74↓	3.81↓	15.36* ↓	1.87 ↑	17.45 ↑
	HDL	03.95↓	04.05↓	00.46↓	01.53↓	4.73↑	1.78↑	5.59* ↑	06.40↓	2.69↓
	SGOT	14.14*↓	09.52*↓	02.34↑	02.09↓	9.24 ↓	1.24 ↓	5.02 ↓	00	0.90↑
	SGPT	13.16*↓	10.88↑	07.72↓	03.63↑	10.72 ↓	NSD	NSD	5.89 ↑	11.73↑
	Alkaline phosphatase	08.30↑	04.40↑	05.52↑	11.99↑	8.24 ↑	NSD	NSD	2.96 ↑	0.73 ↑
	Bl. Urea	01.27↑	05.87↑	09.73↓	01.21↓	5.87 ↓	6.24↓	9.7↓	0.48↓	21**↓
	S. creatinine	08.15*↓	04.67↑	09.06↓	02.73↑	2.47 ↓	8.15 ↓	2.52 ↓	01.60↓	0.93↓
	S. protein (T)	00.36↑	00.36↑	00.31↑	00.17↓	4.11↑	7.49*↑	7.92↑	4.51 ↑	0.47 ↓

↓ = Decrease, ↑ = Increase, NSD = P< 0.05 (non significant decrease), * = P<0.01 (significant), ** = P<0.001 (highly significant).

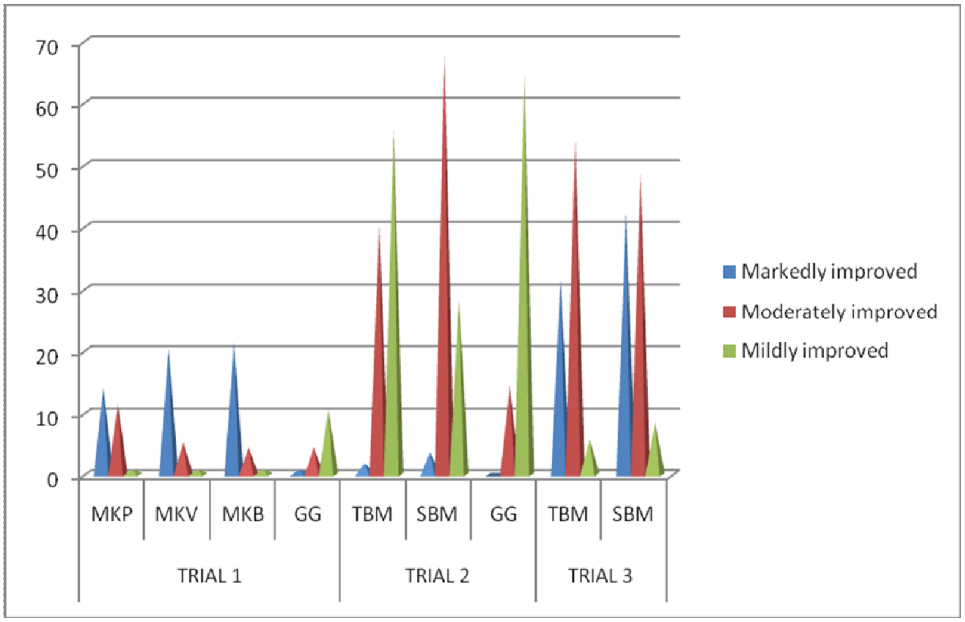

Figure 1. Overall effect of therapy of all three studies