ORIGINAL ARTICLE

Evaluation of Antihyperglycemic and Hypoglycemic Activities of *Shadguna Makaradhwaja* and *Guduchi Ghana* in Swiss Albino Mice

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Abstract

Background: Diabetes mellitus (DM) is a group of metabolic disorders which share the common phenotype of hyperglycemia that occurs due to defects in insulin secretion, insulin action, or sometimes both. Herbomineral formulations can be the alternative for contemporary synthetic oral hypoglycemic agents due to their potency, suitability, and negligible side effects. *Makaradhwaja* is one of those potent antidiabetic drugs used in Ayurved.

Objectives: To evaluate the hypoglycemic and antihyperglycemic activity of *Shadguna Makaradhwaja* (SM) formulations prepared by *Swarna Varkha* (SMV) and from residue *Apakwa Talastha Swarna* powder (SMR) with *Guduchi Ghana* (GG) in Swiss albino mice.

Materials and methods: Oral glucose tolerance test and 18 hours fasted mice model were used. *Shadguna Makaradhwaja* with GG (5.85:94.15 ratios) was administered with honey at a dose of 65 mg/kg. Glibenclamide (GB; 0.65 mg/kg) was used as the standard drug.

Results: In hypoglycemic study, SMV showed 18.2, 27.83, 34.88, and 47.41%, while SMR showed 4.85, 20.52, 29.70, and 44.3% reduction in blood sugar level (BSL) at 1, 2, 3, and 5 hours, respectively. In antihyperglycemic study, SMV showed 81.73, 49.23, 14.8, and 0% and SMR showed 56.38, 42.23, 1.16, and 21.58% reduction in BSL at 30, 60, 90, and 120 minutes, respectively. Both results were statistically significant when compared to the control group.

Conclusion: Test drugs showed significant hypoglycemic and antihyperglycemic effects as compared to the control group. SMV showed more hypoglycemic effect, while SMR showed better antihyperglycemic effect.

Keywords: Ayurved, Diabetes mellitus, Herbomineral, *Makaradhwaja*, *Rasashastra*.

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders, which share common phenotype of hyperglycemia that occurs due to defects in insulin secretion, insulin action, or sometimes both.[1] Nowadays DM is one of the leading cause of morbidity and mortality.[2] Many herbomineral drugs possess the potential of lowering BSLs, and these are found effective when tested in experimental animal models.[3] *Makaradhwaja* is one such well-known herbomineral preparation used by Ayurvedic fraternity due to its therapeutic properties to combat *Madhumeha* (DM).[4–6] *Makaradhwaja* is a herbomineral drug prepared by *Kupipakwa* method.[7] *Shadguna Makaradhwaja* (SM) is said to be superior to *Dwiguna* and *Triguna Makaradhwaja* as *Balijarana* potentiate the therapeutic efficacy of the drug.[8] *Guduchi* (*Tinospora cordifolia* L.) is reported to be a potent antidiabetic drug in Ayurved.[9] *Guduchi*, a well-known anti-hyperglycemic drug according to Ayurvedic classics,[10] also acts as an antioxidant, immunomodulator, and a rejuvenator.[11] The dried aqueous extract of *Guduchi* is used with *Sindur Kalpana* in DM.[12] Different texts of Ayurved have mentioned antidiabetic properties of honey.[13] Honey acts as a vehicle drug (*Yogavahi*) when mixed and used with herbomineral formulations.[14] It is used as a vehicle drug with *Makardhwaja*.[15] For dose formation, honey is used as a liquid media to prepare suspension. It has been found effective in DM also.[6]

The *Balijarana* (addition of sulfur for digestion) and *Ashtasamskaras* (eight processes to purify mercury) are given much importance in the field of Rasashastra (iatrochemistry), but no work is reported till date with use of *Talastha Swarna* powder (bottom residue). Shadguna Makaradhwaja was prepared by two methods using SMV as well as SMR powder (residue at the bottom) form.

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The study may provide leads to assess the role of gold form in the preparation of SM used for DM. Keeping this in view, an attempt has been made to compare both the forms of SM, viz., SMV and SMR, for their antihyperglycemic and hypoglycemic activities.

Materials and Methods

Test Drugs

SMV and SMR were prepared in *Rasa Shastra* and *Bhaishajya Kalpana* department, IPGT and RA, Jamnagar, Gujarat, India, by adopting the standard manufacturing procedures. Two samples of SM, viz., one from SMV (thin foils of gold) and other prepared from SMR powder (bottom residue) were prepared in the ratio of 1:8:48 [ratio of *Swarna* (Au), *Parada* (Hg), and *Gandhaka* (S)] and subjected to *Kupipakwa* through vertical electric muffle furnace for 36 hours.[16] Honey which was used as a vehicle control was of Indian Honey marketed by Azad Khadi Gramodyoga Bhandar, approved by Government of India and was easily available. Fresh *Guduchi* (*Tinospora cordifolia* Miers) stems spreading over *neem* (*Azadirachta indica* A. Juss.) trees were collected from the campus of Gujarat Ayurved University for the preparation of *Guduchi Ghana* (GG).[17]

Animals

Swiss albino mice of either sex weighing 30 ± 5 g were used in the experimental study. Animals were obtained from the animal house attached to Pharmacology Laboratory of Institute, IPGT and RA, Gujarat Ayurved University, Jamnagar, for experiments and maintained under standard experimental and husbandry conditions. The animals were housed in cage made of polypropylene with stainless steel top grill. The dry wheat (post hulled) waste was used as the bedding material and was changed every morning. The animals were exposed to 12-hour light and 12-hour dark cycle with the relative humidity of 50 to 70% and the ambient temperature during the period of experimentation was 22 ± 03°C. Animals were fed with Amrut brand rat pellet feed supplied by Pranav Agro Mills Pvt. Limited and drinking water *ad libitum*. Experiments were carried out after obtaining the permission from Institutional Animal Ethics Committee (IAEC/16/2014/04).

Dose Selection and Schedule

The classics of *Rasashastra* describe the dose of *Makaradhwaja* from 1 *Ratti* (125 mg) to 2 *Ratti* (250 mg),[18] where the dose of *Makaradhwaja* comes as 14.63 mg. *Shadguna Makaradhwaja* has been given twice a day along with GG and honey as *Anupana* (vehicle).[19] Hence, the final human dose of *Makaradhwaja* is 14.63 mg along with 235.37 mg of GG twice a day. Dose was calculated by extrapolating the human dose to animals based on the body surface area ratio[20] which comes out to be 65 mg/kg body weight of mice. Test drugs were mixed in honey and distilled water in suitable concentration to make the suspension and administered to animals by oral route with gastric oral cannula according to their respective body weight. A total of 42 mice were selected for the experiment. Animals were divided randomly to relevant groups of six each after 7 days of acclimatization. Both activities were then evaluated in the test drug per the following protocols.

Hypoglycemic Activity[21]

Swiss albino mice of either sex were randomly divided into five groups of six each (Table 1). Second group served as a standard control group to which GB (0.65 mg/kg) was administered. Animals were fasted overnight prior to experiment and in the morning the initial fasting BSL was measured with the help of One Touch Ez Smart CE0537 Glucometer (Lifeline Surgicals, New Delhi, India), by using One Touch EzGluco test strips per user guideline after anaesthetizing the animals with ether and collecting the blood sample from the tail vein following aseptic conditions. The vehicle control drug (VC) and GB were administered to the respective groups. The BSL was recorded after 1, 2, 3, and 5 hours of the test drug administration for assessing the hypoglycemic effect.

Table 1: Grouping of animals

Group I	WC	Water control group (10 mL/kg, po)
Group II	GB	Standard control group, glibenclamide (0.65 mg/kg, po)
Group III	VC	Vehicle control group received honey in distilled water
Group IV	SM-V	SM prepared from *Swarna Varkha* + GG (520 mg/kg, po)
Group V	SM-R	SM prepared from bottom residue + GG (520 mg/kg, po)

Antihyperglycemic Activity[21]

Swiss albino mice of either sex were randomly divided into five groups of six each. The animals were fasted overnight prior to experiment and the fasting initial BSL was measured. SMV, SMR, VC, water control group (WC), and GB were given to the respective group of animals per the body weight. After 1 hour of drug administration, glucose (5 g/kg) solution was administered to second, third, and fourth groups orally by dissolving it in distilled water. Thereafter, the BSL was recorded at 30, 60, 90, and 120 minutes of post-glucose overload for assessing the antihyperglycemic activity since glucose solution was given.

Statistical Analysis

The results were presented as mean ± standard error of the mean. Data generated during the study were subjected to Student's "*t*" test for paired and unpaired data to assess the statistical significance, and the significance level was set at $p < 0.05$.

Results

The results of hypoglycemic study proved that GB showed highly significant decrease in blood glucose level (BGL) in overnight fasted animals at all time intervals in comparison to initial as well as WC mice. In hypoglycemic study, SMV showed 18.2, 27.23, 34.88, and 47.41% while SMR showed 4.85, 20.52, 29.70, and 44.3% reduction in BSL at 1, 2, 3, and 5 hours, respectively. The group treated with SMV produced significant decrease in BGL in overnight fasted animals at all time intervals in comparison to initial as well as control group of animals. The group treated with SMR produced significant decrease in BGL at all time intervals in comparison to the initial values and produced significant decrease in fasting blood glucose level after 2 and 5 hours in comparison to the control group of animals. Overall, SMV produced pronounced hypoglycemic effect followed by SMR in normal mice. However, the BGL in drug-treated groups was still within the normal range (Tables 2 and 3).

The results of antihyperglycemic study indicated that GB produced marked and highly significant antihyperglycemic effect in comparison to its initial value as well as WC at all time intervals. SMV showed 81.73, 49.23, 14.8, and 0% and SMR showed 56.38, 42.23, 1.16, 21.58% reduction in BSL at 30, 60, 90, and 120 minutes, respectively. Both SMV and SMR produced significant increase in BGL

Table 2: Effect of test drugs on blood sugar level in normal overnight fasted Swiss albino mice at 1- and 2-hour intervals

Groups	*Initial*	*1 hour*	*% decrease to initial*	*2 hours*	*% change to initial*
WC	119.83 ± 2.24	116.00 ± 4.80	3.28 ± 3.20↓	99.50 ± 4.70**	17.05 ± 3.06↓
GB	103.16 ± 4.96	71.00 ± 13.68*$^{\#\#}$	31.45 ± 12.92↓$^{\#\#}$	59.67 ± 8.61**$^{\#\#\#}$	42.05 ± 8.16↓$^{\#\#}$
VC	103.0 ± 4.73	96.25 ± 9.63	7.17 ± 3.65↓	83.75 ± 5.07**	18.63 ± 1.82↓
SMV	115.33 ± 6.72	93.00 ± 6.154*$^{\#\#}$	18.20 ± 6.98↓$^{\#\#}$	82.67 ± 1.26*$^{\#\#\#}$	27.23 ± 3.3↓$^{\#}$
SMR	100.00 ± 6.92	95.00 ± 10.5*	4.85 ± 5.2↓$^{\$}$	77.80 ± 8.55**$^{\#}$	20.52 ± 5.80↓$^{@}$

Data: mean ± SEM; ↓ decrease; *p < 0.05, **p < 0.02, ***p < 0.01, ****p < 0.001 when compared to respective initial values (paired '*t*' test); $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.02, $^{@}p$ < 0.01, $^{\$}p$ < 0.001 when compared to control group (unpaired '*t*' test)

Table 3: Effect of test drugs on blood sugar level in normal overnight fasted Swiss albino mice at 3- and 5-hour intervals

Groups	*Initial*	*3 hours*	*% change to initial*	*5 hours*	*% change to initial*
WC	119.83 ± 2.24	88.83 ± 4.90**	25.71 ± 4.42↓	78.83 ± 2.85***	34.11 ± 3.08↓
GB	103.16 ± 4.96	47.16 ± 5.90***$^{@}$	53.88 ± 5.95↓$^{@@}$	51.33 ± 5.21***$^{@@}$	50.05 ± 4.93↓$^{\#\#}$
VC	103.0 ± 4.73	78.00 ± 7.80*	24.38 ± 5.21↓	67.00 ± 6.56**	35.37 ± 3.06↓
SMV	115.33 ± 6.72	74.0 ± 3.87*$^{\#}$	34.88 ± 3.9↓$^{\#}$	59.83 ± 1.58***$^{\#\#\#}$	47.41 ± 2.20↓$^{\#\#\#}$
SMR	100.00 ± 6.92	71.833 ± 11.23*	29.70 ± 6.83↓$^{\$}$	55.83 ± 5.95***$^{\#\#\#}$	44.37 ± 3.30$^{\#}$↓

Data: mean ± SEM; ↓ decrease; *p < 0.05, **p < 0.02, ***p < 0.01, ****p < 0.001 when compared to respective initial values (paired '*t*' test); $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.02, $^{@}p$ < 0.01, $^{\$}p$ < 0.001 when compared to control group (unpaired '*t*' test)

Table 4: Effect of test drugs on blood sugar level in glucose overloaded Swiss albino mice at 30- and 60-minutes intervals

Groups	*Initial (mg/dL)*	*30 minutes (mg/dL)*	*% change to initial*	*60 minutes (mg/dL)*	*% change to initial*
WC	97.00 ± 4.21	276.20 ± 7.78****	185.90 ± 8.75↑	155.40 ± 12.45**	92.36 ± 8.71↑$^{\#}$
GB	88.33 ± 3.70	82.00 ± 3.36***$^{\$}$	7.10 ± 1.47↓$^{\$}$	76.66 ± 3.03****$^{\$}$	13.10 ± 1.33↓$^{\$}$
VC	122.33 ± 8.54	243.75 ± 41.55*	97.06 ± 23.73↑$^{@}$	168.25 ± 15.22*	37.97 ± 7.36↑$^{\#\#}$
SMV	94.00 ± 5.52	169.75 ± 8.80***$^{\$}$	81.73 ± 10.73↑$^{\$}$	137.75 ± 7.42*	49.23 ± 15.78↑$^{\$}$
SMR	116.60 ± 6.79	181.80 ± 17.43**$^{\$}$	56.38 ± 13.79↑$^{\$}$	166.80 ± 15.30*	42.23 ± 6.20↑$^{\$}$

Data: mean ± SEM; ↑ increase; ↓ decrease; *p < 0.05, **p < 0.02, ***p < 0.01, ****p < 0.001 when compared to respective initial values (paired '*t*' test); $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.02, $^{@}p$ < 0.01, $^{\$}p$ < 0.001 when compared to control group (unpaired '*t*' test)

Table 5: Effect of test drugs on blood sugar level in glucose overloaded Swiss albino mice at 90- and 120-minutes intervals

Groups	*Initial (mg/dL)*	*90 minutes (mg/dL)*	*% change to initial*	*120 minutes (mg/dL)*	*% change to initial*
WC	97.00 ± 4.21	117.60 ± 3.43*	22.57 ± 8.07↑	106.80 ± 2.76	10.92 ± 5.53↑
GB	88.33 ± 3.70	65.33 ± 1.82****$^{\$}$	25.65 ± 2.41↓	60.00 ± 1.71****$^{\$}$	31.64 ± 2.66↓
VC	122.33 ± 8.54	125.25 ± 1.56$^{@}$	4.52 ± 8.84↑	106.25 ± 3.09*	12.01 ± 4.41↓
SMV	94.00 ± 5.52	106.50 ± 7.71	14.80 ± 11.81↑	93.50 ± 5.31$^{\#}$	–
SMR	116.60 ± 6.79	117.20 ± 4.65	1.16 ± 3.65↑	91.40 ± 8.25$^{\#\#}$	21.58 ± 5.31↓

Data: mean ± SEM; ↑ increase; ↓ decrease; *p < 0.05, **p < 0.02, ***p < 0.01, ****p < 0.001 when compared to respective initial values (paired '*t*' test); $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.02, $^{@}p$ < 0.01, $^{\$}p$ < 0.001 when compared to control group (unpaired '*t*' test)

at 30 and 60 minutes in glucose overloaded mice in comparison to the initial values but the magnitude was much less and produced highly significant antihyperglycemic effect in comparison to glucose overloaded WC. After 90 minutes, the BGL reached almost near to initial values in SMR-treated groups; and after 120 minutes, marked decrease in BGL was observed in comparison to the initial values in glucose overloaded mice. SMV-treated group showed increase in BGL after 90 minutes; however, the magnitude was less in comparison to the control group, but after 120 minutes BGL reached almost near to initial values in SMV-treated groups (Tables 4 and 5).

Discussion

Hypoglycemia is an abnormally diminished content of glucose in the blood.[22] Hypoglycemia also occurs as a complication of treatment of DM with insulin or oral medication. Hypoglycemic potential of both samples of SM were compared with the reference standard drug (GB) in which the most frequently reported side effects are gastric disturbances such as nausea, vomiting, heartburn, anorexia, and increased appetite after its oral therapy.[23] The measurement of BSL is generally not a very accurate method. Although used for comparison purposes, the adopted method seems to be useful.

The mechanism to be noted and also the common mode of action is insulinotrophic effect. These drugs promote insulin secretion from the β-cells of islet of Langerhans.[24] Drugs with this mechanism of action have the tendency to produce hypoglycemia if the dose is increased and also in normoglycemic animals. So, such drugs produce good hypoglycemic activity even in normoglycemic mice.

Recently drugs with α-glucosidase inhibitory effects have also been introduced. The basis for their development was the fact that in the intestine only the monosaccharides such as glucose

and fructose can be transported from the intestinal lumen into the blood stream. Hence, complexes such as starches, oligosaccharides, and disaccharides must be first converted to monosaccharide molecules before they are absorbed from the intestine. The enteric enzymes α-amylase and α-glycosidase that are attached to the intestinal brush border catalyze the breakdown of the complex sugars to monosaccharide. If their activity is inhibited, the intestinal absorption of the carbohydrates would be decreased. This will lead to fall in the BSL. This will result in insulin sparing effect.[25] The test drug needs to be assessed for this effect.

It is obvious from data that metformin (GB) is a better hypoglycemic agent as compared to both the Ayurvedic preparations. Overall, SMR produced pronounced antihyperglycemic effect followed by SMV in glucose overloaded hyperglycemic mice. However, the BGL in drug-treated groups reached normal range after 90 minutes and remained in normal range even after 120 minutes.

Both the drugs produced hypoglycemic and antihyperglycemic effect in mice. SMV showed more hypoglycemic effect, while SMR showed more antihyperglycemic effect statistically. It infers that the drugs may show high glycemic lowering activity in empty stomach. Ayurvedic classics also advocate using antidiabetic drugs in empty stomach. It is quoted that if drug is taken empty stomach (before meal), the therapeutic effect of drug increases.[26] Contemporary evidences also support these ancient claims.[27] Honey also has been mentioned as a novel antidiabetic agent;[28] but nowadays due to adulteration, it is not prescribed for patients with glucose intolerance. Evidence suggests that fructose consumption prolongs gastric emptying,[29] which may slow down the rate of intestinal absorption.[30] In addition to fructose, oligosaccharides such as palatinose (isomaltulose) present in honey have been reported to delay digestion and intestinal absorption of glucose resulting in reduced glycemia.[31,32] In case of *Makaradhwaja*, it is chemically sulfides of mercury (HgS) which are well absorbed in stomach in the presence of gastric juice in very minute quantity. But no evidence of mercury was found as traces in the body fluids after absorption of these sulfides. It means only sulfur contents are absorbed in stomach and not mercury, which is excreted with feces.[33] Mercury is said to be a bioenhancer in Ayurvedic pharmaceutical science. In addition to maintaining its own activity, it increases the therapeutic activity of the other substances by many folds.[34] Although the mechanism of its absorption and excretion is still not clearly understood, the exact mechanism needs to be established further. Likewise the action of sulfonylurea group of oral hypoglycemic agents, *Makaradhwaja*, in which sulfur is processed by mercury and gold, may stimulate the beta cells of pancreas which in turn stimulates the secretion of insulin and thus lowers the BSL.[15] Pronounced hypoglycemic effect of *Varkha* might be due to more gold content in the sublimed product, while the anti-hyperglycemic effect may be due to repeated heating as SMR was prepared from residue. It is understood that repeated heating causes stability, which affects the absorption and assimilation of the drug in the body. This fact is also evident by the analytical studies.

Conclusion

Study provided definite evidence for the presence of hypoglycemic and antihyperglycemic activity in SM. However, among two samples, SM prepared with *Varkha* demonstrated better hypoglycemic activity while SM prepared with residue possesses better antihyperglycemic action.

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हिंदी सारांश

स्विस एल्बिनो माइस में षडगुण मकरध्वज एवं गुडूची घन की एंटीहाइपरग्लाइसेमिक और हाइपोग्लाइसेमिक गतिविधियों का मूल्यांकन

पृष्ठभूमि: डायबिटीज मेलिटस चयापचय संबंधी विकारों का एक समूह है जो हाइपरग्लाइसेमिक के सामान्य फेनोटाइप को शेयर करता है जो इंसुलिन स्राव, इंसुलिन कार्य या कभी-कभी दोनों में दोषों के कारण होता है। हर्बोमिनरल फॉर्मूलेशन समकालीन सिंथेटिक ओरल हाइपरग्लाइसेमिक एजेंटों के लिए उनकी क्षमता, उपयुक्तता और नगण्य दुष्प्रभावों के कारण वैकल्पिक हो सकता है। *मकरध्वज* आयुर्वेद में प्रयुक्त शक्तिशाली मधुमेह रोधी (एंटीडायबिटिक) औषधियों में से एक है।

उद्देश्य: स्विस एल्बिनो माइस में गुडूची घन (जीजी) के साथ अपक्व तलस्थ स्वर्ण पाउडर (एसएमआर) के अवशेष से और स्वर्ण वर्ख द्वारा तैयार योग षडगुण मकरध्वज (एसएम) की हाइपोग्लाइसेमिक और एंटीहाइपरग्लाइसेमिक गतिविधियों का मूल्यांकन करना।

सामग्री और विधियां: ओरल ग्लूकोज टोलरेंस परीक्षण और 18 घंटे फास्टेड माइस के मॉडल का प्रयोग किया गया। 65 मिग्रा/किग्रा के एक खुराक में शहद के साथ जीजी सहित षडगुण मकरध्वज (5.85 : 94.15 अनुपात में) दिया गया। मानक औषधि के रूप में ग्लिबेनक्लेमाइड (जीबी; 0.65 मिग्रा/किग्रा) का उपयोग किया गया।

परिणाम: हाइपोग्लाइसेमिक अध्ययन में 1,2,3 और 5 घंटों में क्रमशः एसएमवी ने 18.2, 27.83, 34.88 और 47.41% जबकि एसएमआर ने 4.85, 20.52, 29.90 और 44.3% ब्लड शुगर लेवल (बीएसएल) में कमी पाई गई। एंटीहाइपरग्लाइसेमिक अध्ययन में 30, 60, 90 और 120 मिनट में क्रमशः एसएमवी ने 81.73, 49.23, 14.8 और 0% और एसएमआर ने 56.38, 42.23, 1.16 और 21.58% बीएसएल में कमी पाई गई। नियंत्रण समूह की तुलना में दोनों परिणाम सांख्यिकीय रूप से महत्वपूर्ण थे।

निष्कर्ष: नियंत्रण समूह की तुलना में परीक्षण औषधियों ने महत्वपूर्ण हाइपोग्लाइसेमिक और एंटीहाइपरग्लाइसेमिक प्रभाव दर्शाए। स्वर्ण वर्ख ने अधिक हाइपोग्लाइसेमिक प्रभाव जबकि एसएमआर ने एंटीहाइपरग्लाइसेमिक प्रभाव दर्शाए।

मुख्य शब्द: आयुर्वेद, डायबिटीज मेलिटस, हर्बोमिनरल, मकरध्वज, रसशास्त्र।