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TITLE

Evaluation of Anti - Hyperglycaemic activity of *Madhu* (Honey) in High fat diet induced diabetes - An Experimental study

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ABSTRACT

Background: *Madhu* (honey) is the only natural sweetener available since ancient times. It is used both as a food and medicine since ages. Ayurveda literature emphasises *Madhu* as *Sarvapramehahara* (curer of all types of *Prameha*) and is indicated in the management of *Kaphaja Vyadhi* (diseases caused due to *Kapha Dosha*) and *Sthoulya* (Obesity) due to *Medo Dhatu Vruddhi* (increase in adipocyte mass). **Aim:** The study is aimed at evaluating the anti-hyperglycaemic activity of *Madhu*. **Materials and Methods:** Study was conducted on STZ (streptozotozin) /HFD (High fat diet) induced diabetes in obese wistar albino rats. *Madhu* mixed with *Triphala Kashaya* (*Samyoga*) and processed with *Triphala Kashaya* (*Samskara*) was administered for 30 days as per dose conversion formula. Reduction in body weight, blood lipid profile and blood sugar levels were recorded and statistically compared with control, high fat diet group and other groups treated with *Kevala Madhu* (only honey), *Jala Samskaarita Madhu* (honey processed with water) and standard drug (Pioglitazone). **Results:** Initial reduction in body weight and serum glucose levels was observed in all treated groups. *Triphala Kashaya* mixed with *Madhu* treated animals exhibited significant regain of body weight and reduction in serum glucose, serum cholesterol and triglycerides concentration. **Conclusion:** The study reveals significant anti-hyperglycaemic activity associated with anti-hyper cholestraemic activity of *Madhu* mixed with *Triphala Kashaya* (*Samyoga* group) compared to *Samskaritha Madhu* (processed honey group).

Keywords: *Anti-hyperglyceamic activity, HFD (High fat diet), Madhu (Honey), Triphala, Samyoga and Samskara, STZ (Streptozotozin)*

Introduction

Life style diseases are the most discussed health risks of present era due to causation of more number of deaths compared to other conditions worldwide, involving conditions like diabetes, hypertension, cancer, obesity and varieties of metabolic disorders. [1] By 2030, the prevalence of diabetes is predicted to double globally with a maximum increase in India which may afflict 79.4 million individuals. [2] Obesity increases risk of Type 2 Diabetes mellitus. [3] In overweight individuals, adipose tissue becomes dysfunctional and leads to reduced insulin sensitivity [4] and moreover insulin resistance and Type 2 Diabetes mellitus are characterised by dyslipedaemia. [5] Classical literatures of Ayurveda caters detailed narration about involvement of *Medodhathu* in both *Sthoulya* (Obesity) and *Prameha* (Diabetes) [6] as both entities are *Santarpanotthavyadhis* (diseases caused due to over nutrition) [7] and have similar causative factors. Abnormal *Medodhatu* (*Bahuabaddhamedas*) is said to be the primary cause for *Prameha Samprapti*. [8] *Prameha* is further classified into *Sthoola* and *Krisha Pramehi* (Obese & lean diabetes) [9] among which former one needs colloquial management. Therapeutic implications for the long term treatment modalities relay not just upon pharmacotherapy but also involve diet and physical exercise. [10]

Therapeutic modalities in Ayurveda invariably indicate *Madhu* and *Triphala* in both *Prameha* and *Sthoulya*, where *Madhu* with *Triphala Kashaya* is highlighted as *Sarvapramehahara*. [11]

Though *Purana Madhu* (old honey) alone has been attributed with *Lekhanakarma* (scrapping), which is indicated in *Sthoulya*, processing with *Dravyas* having similar activities are mentioned in few texts of Ayurveda. Contradictory statements in classical texts regarding heating of *Madhu* necessitate detailed pre-clinical investigations on safety and efficacy. High fat diet along with low dose streptozotocin induced diabetes model in experimental animals is said to mimic type 2 diabetes in human beings. Hence present study was undertaken to evaluate anti - hyperglycaemic activity of honey in processed and unprocessed forms in Streptozotozin/High fat diet induced diabetes in wistar albino rats.

Materials and Methods

Freshly extracted un-processed honey was obtained from the Bhagamandala Honey society, Kodagu district, Karnataka and was stored in dry amber coloured glass bottles for one year to make it *Purana* (aging process). Streptozotozin was procured from SRL chem-company. Deseeded fruits of *Haritaki* (*Terminalia chebula* Retz), *Vibhitaki* (*Terminallia bellerica* Roxb) and *Amalaki* (*Embellica officinalis* Gaertn) were procured from local market. Fruits were pounded to obtain *Yavakuta* (coarse powder) and mixed thoroughly to obtain *Triphala Choorna* (fine powder).

Kashaya (decoction) was prepared as per standard protocol of Sharangadhara Samhita. *Madhupaka Vidhi* (processing honey) was carried out using *Madhu* and *Triphala Kashaya* in equal proportions as per Kaiyadeva Nighantu with minor modifications. [12] *Madhu* and *Triphala Kashaya* were mixed in equal proportions for *Kashaya Samskara* process where as *Madhu* and water was mixed in the ratio of 8:1 for *Jala Samskara*. Instead of heating *Madhu* directly over flame, water bath at (95^0 C) was used during condensation process to avoid charring of honey. [13] Same procedure was adopted for preparation of *Jala Samskaritha Madhu* (honey processed with water).

Preparation of Normal and High fat diet

High fat diet for wistar albino rats was prepared under standard laboratory conditions. Ingredients of diet [14] (Table 1) were mixed, converted into pellets, dried in hot air oven and stored in cool and dry container.

Table no. 1: Composition of Normal and High Fat Diet

Normal Diet requirement per day per rat		High Fat Diet requirement per day per rat	
Constituents	**Weight in gm**	**Constituents**	**Weight in gm**
Whole Wheat	3.24	Whole Wheat	2.72
Yellow Corn	3	Yellow Corn	2.72
Barley	1.8	Barley	1.36
Milk Powder	1.8	Milk Powder	2.04
Bone Meal	0.12	Bone Meal	0.13
Calcium Chloride	0.12	Calcium Chloride	0.13
Salt	0.12	Salt	0.13
Oil	1.8	Oil	1.36
Vit. B12	0.048	Vit. B12	0.054
		Butter	1.363

Experimental study

Ethical clearance was obtained from Institutional ethics committee, JSS College of Pharmacy, Mysuru (IEAC 210/2016) prior to commencement of the experimental study. Healthy Wistar Albino male rats weighing between 100-150 g were procured from animal breeding facility, department of Pharmacology, JSS College of Pharmacy, Mysuru.

Experimental animals were sorted in 8 groups comprising 6 animals in each group (Table 2). Prior to commencement of experimentation, experimental animals were acclimatised for 15 days under standard laboratory conditions. Regular rat feed and potable water was provided during this period.

Anti-hyperglycaemic study was conducted for 75 days comprising high fat diet administration for 30 days followed by induction of hyperglycaemia with two consecutive doses of Streptozotozin injection (30mg IP) as per standard protocol. [15] After analysing serum glucose concentration, treatment to elicit anti-hyperglycaemic activity was continued for 30 days. Except normal control group animals, other groups received high fat diet ad libitum throughout the study period. After induction of hyperglycaemia test drug was administered simultaneously along with high fat diet. Normal group animals were provided with regular pellets and water.

The standard drug, pioglitazone was administered in the dose of 30 mg/kg. [16] The dose of the test drug (*Kevala Madhu, Jala Samskarita Madhu, Madhu* mixed with *Triphala Kashaya* and *Madhu* processed with *Triphala Kashaya*) was determined and carried out as per the earlier study as *Avaleha Pramana.* [17] Dose for the rat was calculated on the basis of conversion formula. [18] 860mg/200g of honey was fixed as initial dose and calculated periodically based on change in body weight during study period. Distilled water was used as media to administer *Samskaritha Madhu*, whereas group 6 animals received *Madhu* mixed with *Triphala Kashaya* (*Samyoga* group). Group 6 and 8 received *Madhu* mixed with *Triphala Kasaya* and water respectively. Body weight and Blood glucose levels of the animals was recorded before commencement of experiment and on 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th and 10th weeks. Blood was collected from the retro-orbital area on 76th day and serum was subjected to cholesterol and triglycerides estimation. Data was statistically analysed by ANOVA method using Graph pad prism 6 software for assessing level of significance.

Table no. 2: Showing details of experimental groups

Group 1	Normal diet control group
Group 2	High fat diet –untreated Group
Group 3	High fat diet+streptozotozin - untreated group
Group 4	High fat diet + streptozotozin - treated with pioglitazone
Group 5	High fat diet + streptozotozin - treated with *Triphala Kashaya Samskaritha Madhu*
Group 6	High fat diet + streptozotozin - treated with *Triphala Kashaya* with *Madhu*
Group 7	High fat diet + streptozotozin - treated with *Jala Samskaritha Madhu*
Group 8	High fat diet + streptozotozin - treated with *Purana Madhu*

Observation and Results

All animals pertaining to 8 groups remained healthy with normal food and water intake and no abnormal behaviour was noticed during acclimatisation period.

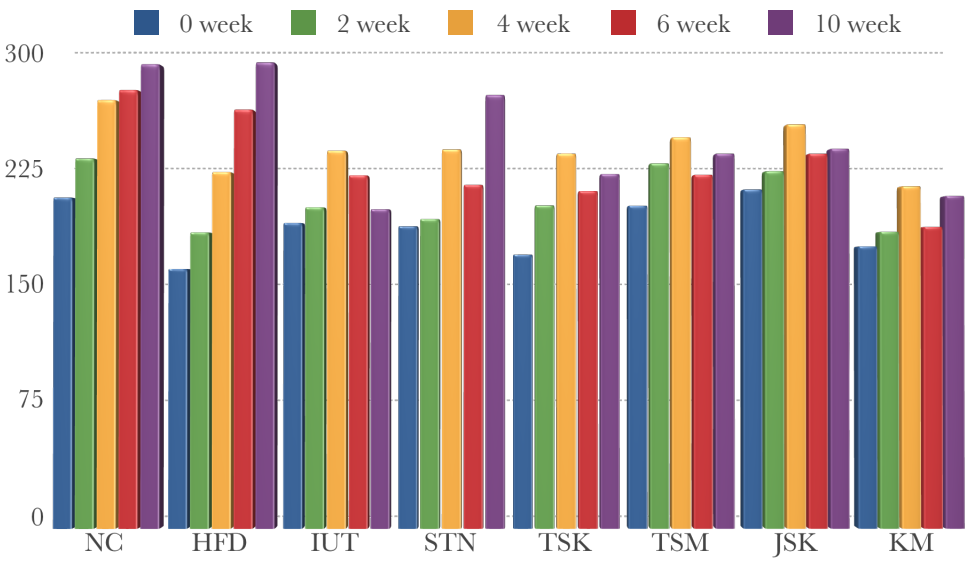
Body weight: (Graph 1)

All animals gained weight till 5th week (before induction of hyperglycaemia) except in control group animals (Normal diet). After administering STZ (except in normal control and HFD group), all other group animals lost weight partially during 5th and 6th week but gained as the treatment continued with different forms of *Madhu* as well as standard drug. Induced untreated group animals continued to loose body weight. Observation made at the end of 10th week (end of experimentation period) revealed gain in the body weight in all treated groups except in induced untreated group. Among treated groups, standard drug treated animals gained bodyweight faster compared to other treated groups and among *Madhu* treated group, *Kevala Madhu* (Unprocessed and without mixing with *Kashaya*) treated group gained relatively more weight of 20-25 gm.

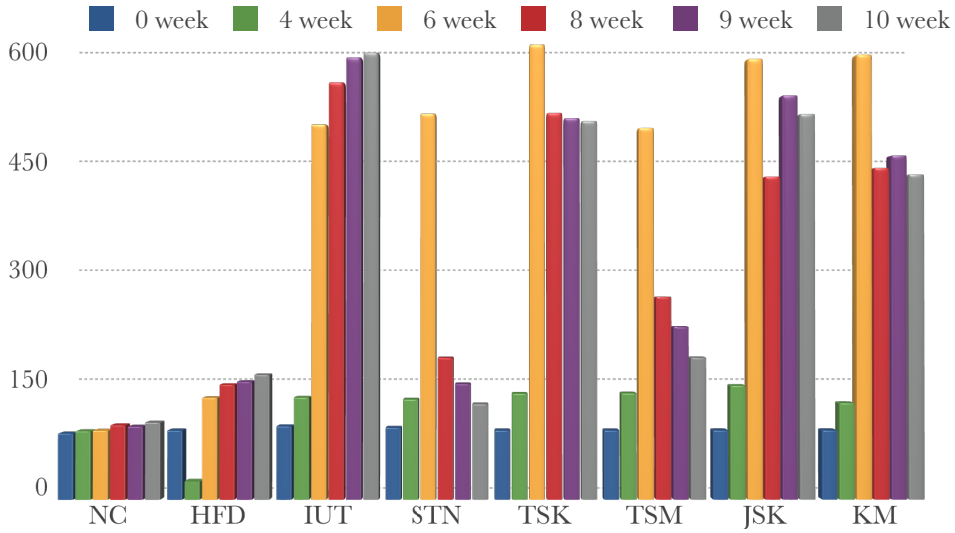
Serum glucose levels: (Graph 2)

After administration of STZ by 5th week, RBS levels of all treated groups as well as induced untreated groups increased considerably and changes were statistically significant compared to control group as well as HFD group (non diabetic). On 7th week, RBS levels reduced marginally in all treated groups. On 8th week, RBS levels among *Triphala Kashaya + Madhu* (TSM), *Jala Samskarita Madhu* (JSK), *Kevala Madhu* (KM) and Standard drug (STN) drug treated animals reduced considerably except in *Triphala Kashaya Samskarita Madhu* (TSK) group. When compared between honey treated groups, RBS levels of TSK group remained higher and TSM at comparatively lower point. At the end of 10th week, TSM and standard drug treated animals had RBS concentrations at relatively lower point and statistically significant ($p<0.05$) compared to TSK, KM, JSK and untreated group animals.

Graph no.1: Body weight (In grams)



Graph no. 2: RBS of all the group (mg/dl)



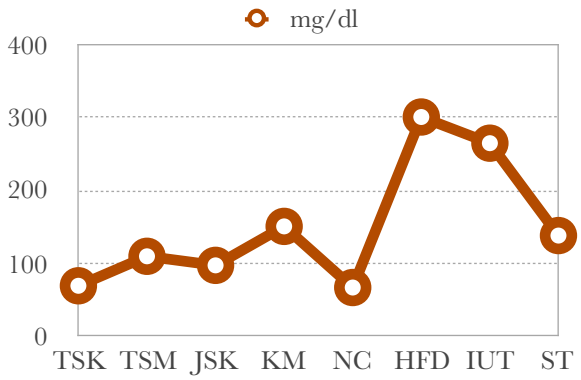
Serum cholesterol: (Graph 3)

Among all treated groups (including standard drug experimental animals), TSK treated group animals showed very low concentration of cholesterol. Among HFD and induced untreated groups, cholesterol concentration remained relatively higher and statistically significant ($p<0.05$) compared to other treated groups and control group.

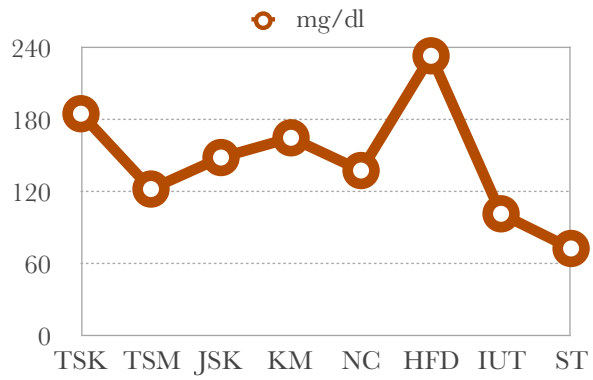
Serum Triglycerides: (Graph 4)

Triglycerides level recorded among all treated groups as well as control group animals at the end of experiment remained at low. Increase in triglycerides level was noticed only in HFD group. Among changes observed between all treated groups and control group, STN drug treated experimental animals showed decrease in triglycerides level but was not significant statistically.

Graph no. 3: Effect on S. Cholesterol (mg/dl)



Graph no. 4: Effect on S.Triglycerides (mg/dl)



Discussion

Honey bees collect nectar from different sources and presence of harmful microbes including *Clostridium botulinulinum* have been reported in few tested samples. [19] Probably such incidents might have prompted honey processing during medieval period. Toxicity due to honey is reported to be reduced after processing. [20] Though *Purana Madhu* alone has been attributed with *Lekhanakarma*, which is indicated in *Sthoulya*, processing with dravyas having similar activities may further potentiate desirable effects. Honey is used as an"*Anupana*" with number of other products due to classically specified "*Yogavahi*" nature.

Heating (processing) method is much debated aspect about honey in both ancient and present eras. Since specific *Madhusamskara* is also mentioned in medieval texts for attaining specific outcomes, testing of processed honey becomes essential over experimental animals to establish safety and efficacy. Earlier studies conducted over effect of different heating temperatures (65^{0}C and 95^{0}C) on HMF content of honey has not revealed much increase of HMF content beyond specified limits. [22]

Pasteurization is carried out to stabilize honey in most of the market samples by using temperature ranging between 72^0–110^0c. Heating honey up to 95^0c has not caused any change in antioxidant activity as reported earlier [13] and hence same temperature was employed in present study protocol. Milliard reaction is the interaction between proteins and sugars of honey, during storage as well as processing. By-products of Milliard reaction are said to bring desirable therapeutic effects [23-24] as milliard reaction products have been shown more antioxidant property. [25] Dark coloured honey samples have exhibited more noteworthy antioxidant activity [26-27] as mentioned in previous works. Present study is based on processed honey with *Triphala Kashaya* which is exerted to maximum anti–hyperlipidaemic potential. [28] Since non diabetic rats were used during previous study on hyperlipidaemia, [28] honey has been proved to act more on diabetic conditions rather non diabetic, [29-30] and induction of hyperglycaemia in high fat fed rats was planned as per established protocol. Previous study conducted on *Samskaritha Madhu* (TSK) had revealed significant anti - hyperlipidaemic potential. Considering previous study findings as well as available facilities and limited time frame, 30 day intervention period was planned [28,22]. Both glucose and fructose have been found playing supportive role with each other i.e. glucose increases absorption of fructose through disaccharide related transport system while fructose enhancing uptake of glucose by liver and muscles resulting in reduction in hyperglycaemia due to activation of enzyme glucokinase, [31-32] which might have played important role in lowering blood sugar in present study. Honey is a complex material having as much as 181 different constituents [33] having maximum amount of oligosaccharides exerting anti- diabetic effect. [34-35] Number of substances like flavonoids, phenolic acids and invert sugar associated with protein enzymes characterise honey constituents has established antioxidant/anti hyperglycaemic and cytoprotective potential, collectively or individually. Differences in anti-obesity and anti-diabetic potential of processed and unprocessed honey have been observed during study period. This may be linked to activation as well as deactivation of specific molecules during processing phase. Elevation in invert sugar and brown pigment tends to increase by heating thereby increasing anti-oxidant activity. [36] Fructose is reportedly delays gastric emptying and thereby delays food intake. Increased phenolic concentration along with elevated fructose concentration must have caused reduction in body weight in TSK treated groups in which honey sample used was much darker. Fructose is found to be stimulating insulin secretion from beta cells. [37]

This together with enzymes such as glucose oxidase, catalase, ascorbic acid and phenolic compounds exert powerful antioxidant activity. [38-39] Heating of honey though elevates fructose content, deactivates most of protein enzymes leading to shift in its efficacy. This might have caused significant anti-hyperglyceamic effect of unprocessed honey mixed with *Triphala Kashaya*. Diabetes mellitus is characterized by impairment in lipid metabolism associated with elevated LDL levels. [40] Disturbances in lipoprotein synthesis in diabetes mellitus [41] further leads to insulin resistance [42-43] through insulin signalling pathway. Previous studies have established efficacy of honey in improving glycemic control through C-peptide mediated insulin secretion and modulation. [44-45] Honey is said to enhance insulin sensitivity in liver and muscle by increased glucose uptake resulting reduction in glycemic condition, [46] Which may be the primary reason in lowering hyperglycaemic condition in test drug treated groups.

Conclusion

Madhu though stored for one year (*Purana Madhu*) will not lead to significant *Lekhana Karma* (reduction in body weight due to reduction in body mass through Shoshana (Drying/Atrophy) as per Sharangadhara Samhita). *Purana Madhu* mixed with *Triphala Kashay*a is a potential anti-hyperglyceamic agent. *Triphala Kashaya Samskaritha Madhu* can be utilized in dyslipedemia in non diabetic conditions but *Samyoga* (mixing) of honey with *Triphala Kashaya* exerts beneficial activity during diabetes associated with dyslipidaemia. Hence, the present study establishes role of *Samyoga* in obesity induced diabetes.

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