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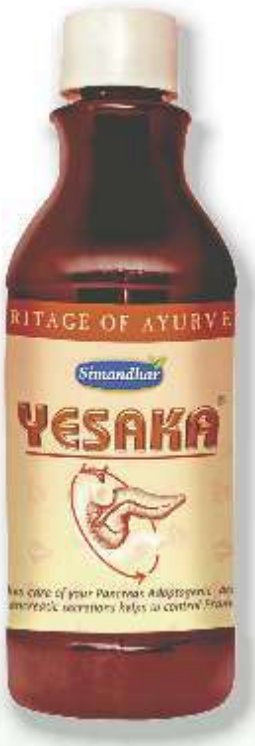

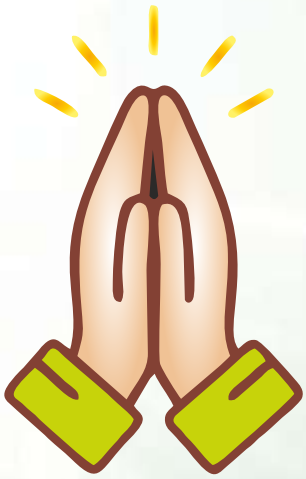

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CLINICAL STUDY: Original Article

Evaluation of Clinical Efficacy and Safety of "Yesaka Liquid" (An Ayurvedic Liquid Formulation) as Add-On Therapy to Oral Hypoglycemic Agents in Type II Diabetes Patients

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Abstract

Introduction: Yesaka Liquid is an Ayurvedic Proprietary formulation containing multiple standardized herbal extracts like Triphala (3 *myrobalans*), Jamun (*Eugenia jambolana*), Kutki (*Picrorhiza kurrooa*), Haridra (*Curcuma longa*) etc., having potential anti-diabetic and anti-oxidant properties. The evaluation of clinical efficacy and safety of Yesaka Liquid as an Add-on therapy to oral hypoglycemic agents (OHAs) in Type II diabetics was the primary objective of the study. **Methods:** After obtaining ethical approval and informed consent, at five study sites, 112 patients were randomized in two study groups. The patients in Add-on Group were given Yesaka Liquid along with OHAs while those in the Control Group were asked to continue with the on-going OHA (s) for 90 days. The assessment of efficacy was done by estimation of HbA1c%, quality of life (QOL) on WHO-QOL BREF questionnaire, plasma glucose, serum insulin, symptoms of diabetes mellitus, anthropometric measurements, and changes in homeostatic model assessment for insulin resistance score. The assessment of safety was done by clinical review of all safety parameters and safety-related laboratory parameters. Global assessment of overall safety and tolerability by the physician and patient was also done. **Results:** Yesaka liquid was found to be effective as add-on therapy to OHAs in type II DM management by controlling the levels of HbA1c and blood sugar. It showed significant effect in reducing various symptoms of type II DM and also improved the QOL of patients. **Conclusion:** Yesaka Liquid can be recommended as an effective and safe formulation for the management of type II DM as an odd-on therapy.

Keywords: *Add-on therapy, herbal extracts, oral hypoglycemic agent*

Introduction

Diabetes mellitus (DM) is one of the metabolic disorders of various causative factors. It is characterized by chronic hyperglycemia along with disturbances in carbohydrate, fat and protein metabolism which results from defects in insulin secretion and/or action.[1] The worldwide prevalence of diabetes in 2019 was estimated to be 9.3%, growing to 10.2% by 2030 and 10.9% by 2045. The worldwide prevalence of impaired glucose tolerance is also growing year by year.[2] The WHO has anticipated that Diabetes will be growing rapidly in India. Diabetes intensifies the risk of premature death.[3]

Diabetics are at high risk of cardiovascular, peripheral vascular and cerebrovascular diseases.[4] oral hypoglycemic agents (OHAs), insulin and lifestyle management are employed in the management of DM. Drugs for treating type II DM include insulin secretagogues, insulin sensitizers and drugs that mainly affect absorption of glucose. Long-term use of these drugs is associated with numerous sides effects such as weight gain, nausea, distension of abdomen, and loose motions.[5,6]

The Ayurvedic description of *Prameha* has a resemblance to the modern-day DM. The prominent symptoms of *Prameha* mentioned is Ayurveda is frequent turbid micturition and presence of sugar/sweetness in urine.[7] A variety of herbs, herbal combinations as well as herbomineral formulations mentioned in Ayurveda are beneficial for the treatment of diabetes These herbs and formulations used as anti-diabetic medications have shown

How to cite this article: Godatwar P, Deshpande S, Tamoli S, Pande S, Hartalkar A, Kulkarni A, *et al.* Evaluation of clinical efficacy and safety of "Yesaka Liquid" (an ayurvedic liquid formulation) as add-on therapy to oral hypoglycemic agents in Type II diabetes patients. J Ayurveda 2022;16:4-10.

Submitted: 24-Mar-2021 **Revised:** 28-Jul-2021
Accepted: 05-Aug-2021 **Published:** 19-Mar-2022

Access this article online

Website: www.journayu.in

DOI: 10.4103/joa.joa_79_21

Quick Response Code:

significant effect on lowering blood sugar levels with minimal or no side effects.[8] These drugs also improve general debility along with providing antioxidant activity much needed in diabetics.

Yesaka Liquid, an Ayurvedic formulation with multiple standardized herbal extracts like Triphala (3 *myrobalans*), Jamuna (*Eugenia jambolana*), Kutaki (*Picrorhiza kurrooa*), Haridra (*Curcuma longa*) etc., is developed by Simandhar Herbals Pvt. Ltd., Mumbai. These ingredients have been individually tested and have been found to have hypoglycemic and anti-oxidant effects. Looking at the activities of the ingredients present in Yesaka Liquid, a hypothesis was postulated that Yesaka Liquid would be beneficial in the management of Type II DM. The present clinical study was planned with an objective to evaluate efficacy and safety of Yesaka Liquid as an add-on therapy to OHAs in Type II Diabetic patients.

Materials and Methods

Study design, sites

This randomized, multi-center, open labelled, comparative, prospective clinical study was carried out at five study sites over India, namely (1) Ayurved Sansodhan Vibhag, Ayurved Seva Sangh, Nashik, Maharashtra, (2) MAMs SS Ayurveda Mahavidyalaya and Sane Guruji Arogya Kendra, Hadapsar, Pune, Maharashtra, (3) National Institute of Ayurveda, Jaipur, Rajasthan, (4) S. D. M. College of Ayurveda, Udupi, Karnataka, and (5) Parul Ayurveda Hospital, Parul University, Vadodara, Gujarat.

Ethical considerations

Ethical approvals from Institutional Ethics Committees of all study centers were obtained. The study was registered on Clinical Trials Registry India (CTRI) vide registration number, CTRI/2019/05/019452 registered on May 30, 2019.

Enrolment of patients

Patients, suffering from type II DM attending the outpatient department of the study centers and who consented, were considered for the study. The study was carried out and reported adhering to CONSORT statement.

Study duration and visits

The total duration of the study treatment was 3 months (90 days). Patients were asked to visit study site every 30th day (±5 days) for 3 months. Patients were evaluated for efficacy and safety assessment by clinical examination and various scales.

Inclusion criteria

Patients of either sex in the age group of 20–70 years (both inclusive) suffering from Type II DM for more than one year and stabilized on mono/polydrug anti-diabetic therapy (OHAs) for at least last 3 months, having HbA1C value between 7% and 11% (both inclusive) at screening visit, having Fasting Plasma Glucose between 126 and 252 mg/dl (both inclusive) at screening visit were included in the study. Furthermore, patients whose electrocardiogram (ECG) did not demonstrate any signs of uncontrolled arrhythmia/acute ischemia and X-ray chest did not show any active lesion of tuberculosis and who voluntarily provided written informed consent and were willingly ready to follow procedures as per the study protocol were included in the study.

Exclusion criteria

Patients on insulin therapy, suffering from type-1 DM or type of DM other than type-2 with known history of chronic hepatic or renal disease, active malignancy, significant cardiovascular event at least 12 weeks prior to randomization were excluded. In addition, patients with major complications of diabetes, contagious infectious diseases, active metabolic or gastrointestinal diseases that may interfere with nutrient absorption, metabolism, or excretion, excluding diabetes were excluded from the study.

Laboratory and radiological investigations

Laboratory investigations of all recruited patients such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), Hb%, fasting and post prandial blood sugar levels, serum insulin, glycosylated haemoglobin (HbA1C%), liver function tests (LFTs), renal function tests (RFTs), lipid profile, urine examination were carried out.

Treatment groups

Eligible patients were randomized (1:1; block randomization) to one of the two groups, i.e. add-on group and control group. Patients enrolled in add-on group received Yesaka Liquid along with OHAs while patients in the control group were asked to continue with the ongoing OHAs.

Details of investigational product

Yesaka Liquid, a polyherbal is proprietary formulation prepared from multiple standardized ingredients including *Triphala, Jamun, Kutaki*, *Haridra* etc., [Table 1]. Patients in the add-on Group were advised to take 20 ml Yesaka Liquid twice daily orally on empty stomach with lukewarm water for 90 days.

Assessment parameters

The assessment of efficacy was done by change in HbA1c % (glycosylated hemoglobin%) level, quality of life (QOL) on WHO-QOL-BREF questionnaire, plasma glucose levels, sr. insulin levels, symptoms of diabetes, body weight, body mass index, waist circumference, and waist to hip ratio, changes in homeostatic model assessment for insulin resistance (HOMA-IR score) from baseline to end of study 90 days in all participants. The assessment of

Table 1: Composition of ingredients in "Yesaka Liquid"

Drug name	Latin name	Form	Each 5 ml contains (mg)
Amalaki	*Phyllanthus emblica*	Extract	80
Haritaki	*Terminalia chebula*	Extract	80
Bhibhitaka	*Terminalia ballerica*	Extract	80
Jamun	*Eugenia jambolana*	Extract	80
Kutaki	*Picorhizakurroa*	Extract	80
Kiraatatikta	*Swertiachirata*	Extract	80
Guduchi	*Tinosporacordifolia*	Extract	80
Gudmar	*Gymnena Sylvester*	Extract	80
Haridra	*Curcuma longa*	Extract	80
Saptachakra	*Salacia chinesis*	Extract	120
Mahanimba	*Melia azardirachta*	Extract	80

Preservatives: Methyl paraben, IP: Sodium benzoate, IP: Propyl paraben IP

dose of OHAs, overall efficacy on CGI-I, Subject's Global evaluation for overall change were also done.

Safety was assessed by clinical review of all safety parameters; such as clinical examination, assessment of posttreatment changes in laboratory parameters (including CBC, ESR, Hb%, LFTs, RFTs, lipid profile, urine examination and ECG). Assessment of Overall Safety and Tolerability of the product by the physician and subject on global assessment scale by the investigator and by subject were also done.

Sample size

Out of total of 112 patients included in study, 68 patients were enrolled in add-on group whereas 44 patients in control group. A total of 12 subjects dropped out from the study, of which 2 subjects were dropped in add-on group while 10 subjects dropped in control group. All these subjects dropped out due to lost to follow-up. A total of 100 subjects completed the study. For the purpose of evaluation 41 subjects in add-on group and 34 subjects in control group were considered as evaluable cases as 25 patients were observed to be noncompliant to the study protocol [Figure 1].

Statistical methods

All demographic details were summarized descriptively. All continuous variables were presented using mean ± standard deviation whereas all categorical variables using actual numbers (n) and percentage (%). The data were analyzed using GraphPad InStat Version 3.6 (www.graphpad.com) software. Normality of data was assessed using Shapiro Wilko test. Data in a group at two intervals were compared using paired *t*-test (data with normal distribution)/Wilcoxon signed-rank test (data with nonnormal distribution). The inter-group comparison was done by unpaired *t*-test (data with normal distribution)/Mann–Whitney test (data with non-normal distribution). The level of significance was set at 0.05,

Observations and Results

Demographic details

The mean age of subjects in the add-on group was 55.51 ± 8.08 years and control group was 56.29 ± 8.94 years which showed statistically insignificant difference ($P > 0.05$). In Add-on Group, out of 41 subjects, there were 26 males (63.41%) and 15 females (36.58%) while in Control Group, out of 34 subjects, there were 21 males (61.76%) and 13 females (38.23%).

Assessment of therapy-primary objectives

1. Assessment of change in HbA1c % over 3 months: In add-on Group, the mean HbA1c% at baseline visit was 8.40% that significantly reduced to 7.82% ($P < 0.05$) at the end 90 days. In the control group, the mean HbA1c% at baseline visit was 8.60% which nonsignificantly reduced to 8.45% ($P > 0.05$) at the end of 90 days. Comparative assessment between the groups showed a better reduction in HbA1c in add-on group though the same was nonsignificant ($P = 0.07$)
2. Assessment of QOL on WHO QOL BREF questionnaire: Comparative analysis between the groups for physical, social health, environmental health, overall QOL and general health showed no significant difference ($P > 0.05$) from baseline visit and all follow-up visits ($P < 0.05$) except Psychological Health. Comparative analysis of Psychological Health between the two groups showed a significant difference between the two groups ($P < 0.05$) where Control Group showed better improvement in psychological health domain score as compared to control group.

Secondary objectives

1. Fasting blood sugar level: In add-on group, the mean fasting blood/plasma sugar level at baseline visit was 153.75 ± 39.21 mg/dl) which significantly reduced ($P < 0.05$) to 136.98 ± 60.84 mg/dl on day 90. In the control group, nonsignificant change was seen in the mean fasting blood sugar level on day 90 (159.36 ± 70.4 mg/dl) compared to baseline visit (148.83 ± 45.58 mg/dl). The reduction in blood sugar levels was found to be statistically significant ($P < 0.05$) in add-on group as compared to the control group
2. Post prandial blood sugar level: In add-on group, the mean postprandial blood/plasma sugar level at baseline visit was 243.42 ± 70.68 mg/dl which significantly reduced ($P < 0.05$) to 200.25 ± 72.38 mg/dl on day 90. In control group, nonsignificant change was seen in the mean fasting blood sugar level on day 90 (232.71 ± 95.54 mg/dl) compared to baseline visit (256.16 ± 83.26 mg/dl). Comparative

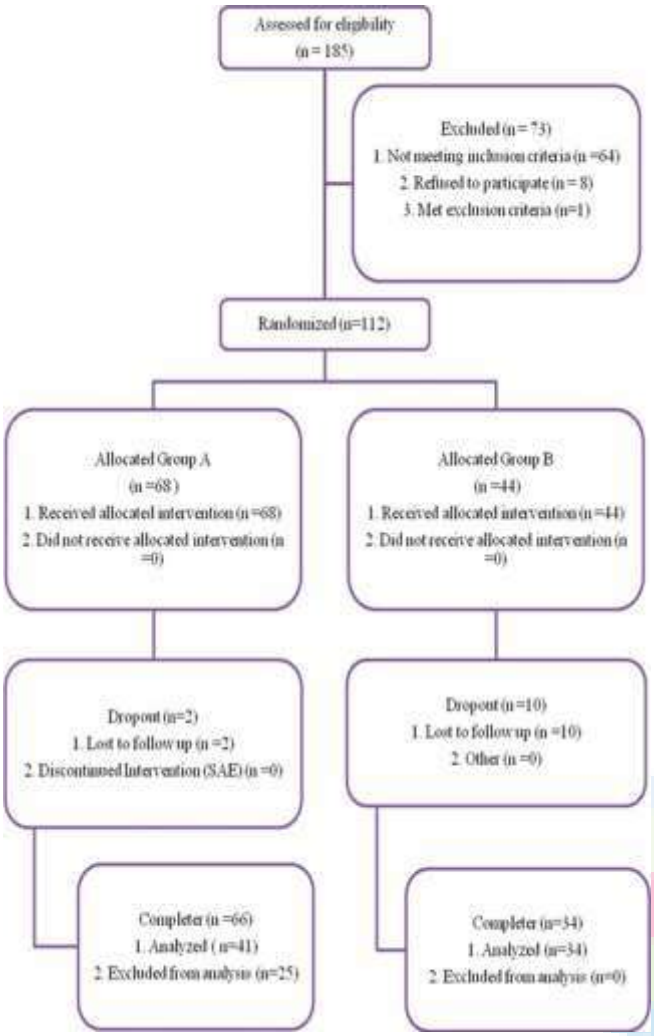

Figure 1: CONSORT statement

analysis between the groups showed nonsignificant difference ($P > 0.05$) in reduction in blood sugar from baseline to day 90

3. Serum insulin level (fasting): In add-on group, the mean serum insulin (fasting) level at baseline visit was 9.28 µU/ml that slightly increased to 9.7 µU/ml ($P > 0.05$) at the end of the study, which was found to be nonsignificant. In control group, the mean serum insulin (fasting) level at baseline visit was 8.25 µU/ml that remained same, i.e., 8.25 µU/ml at the end of the study. Comparative analysis between the groups showed nonsignificant difference ($P > 0.05$) from baseline to day 90
4. Clinical symptoms of DM: The relief in the clinical symptoms of DM like polyuria, polyphagia and polydipsia was found to be statistically significant ($P < 0.05$) in Add-on Group as compared to the Control Group at the end of the study whereas fatigue symptom did not show significant difference ($P > 0.05$) between two groups
5. Assessment of HOMA IR score: The changes in Mean HOMA IR score were found to be non-significant from baseline to the end of the study in both the study groups. When compared between the groups, no significant difference ($P > 0.05$) was observed from baseline visit to 90 days
6. Assessment of monthly change in dose of OHAs between the groups: A total of 3 subjects in add-on group required reduction in OHA dosage while one subject required increase in dose. In the control group, the dose and type of OHA was not reduced in any of the subjects while 4 subjects required increase in dose. The dose in the remaining subjects remained unchanged in the two groups. There was no statistically significant difference on the increase or decrease of dose of OHA between the two groups
7. Assessment of anthropometric measurements: Anthropometric measurements showed no statistically significant difference between the two groups at the end of the study (90 days)
8. Global Assessment of overall change as per the investigator: A total of 25 subjects (60.97%) subjects showed minimal to very much improvement in Add on Group while 15 subjects (44.11%) showed minimal to very much improvement in the control group. Nine subjects (21.95%) in Add on group and 15 subjects (44.11%) in the control group showed no change on global assessment as per the investigator. 7 subjects (17.07%) in Add on group and 5 subjects (14.70%) in control group showed minimal worsening of their condition
9. Global assessment for overall change as per subject: A total of 26 subjects (63.41%) subjects showed minimal to very much in Add on Group while 14 subjects (41.17%) showed minimal to very much improvement in the control group. 10 subjects (24.39%) in Add on group and 15 subjects (44.11%) in the control group showed no change on global assessment as per the subject. Five subjects (12.19%) in add on group and 5 subjects (14.70%) in control group showed minimal worsening of their condition.

Assessment of safety

Evaluation of adverse events/serious adverse events (safety evaluation)

There was a total of 38 AE reported in the study of which 16 were reported in add-on group and 22 in the control group. The common AEs reported were cough, cold, fever, back ache etc., None of the AEs was reported due to the use of study drug (add-on group). All the AEs got resolved with treatment and did not require stoppage of the study drug. One SAE reported in the study (Severe Lower Respiratory Tract Infection) was not related to the study drug or procedure.

There was no significant change in safety-related laboratory parameters including Liver functions, Renal functions, CBC, Lipid Profile, and ECG from baseline to 90 days'

follow-up. These parameters remained within the normal range at both baseline and final visits.

Discussion

The study was carried out to evaluate efficacy and safety of Yesaka Liquid as an Add-on therapy to OHA in type ii diabetic patients. Known cases of DM having HbA1c between the ranges of 7%–11% were recruited after the evaluation of inclusion/exclusion criteria. There was a significant reduction in HbA1c% levels in subjects taking Yesaka Liquid along with OHA over a period of 90 days while subjects taking only OHA showed no significant change in these levels from baseline to 90 days. Comparative assessment between the groups showed a better reduction in HbA1c though the same was nonsignificant ($P < 0.07$). Furthermore, a statistically significant reduction in fasting and post prandial blood glucose levels was observed in subjects of Add on group from baseline to 90 days. The change was found to be non-significant in subjects in the Control group. Comparative assessment between the groups showed the reduction in fasting blood sugar was significantly better in add on group as compared to control group. Comparative assessment of post prandial blood sugar however showed nonsignificant change between the groups.

Serum insulin levels showed no significant change from baseline to 90 days in both the groups and comparative assessment between the groups also showed insignificant difference. Also, there was no statistically significant difference in HOMA IR levels between the groups.

Symptoms of diabetes such as polyuria, polydipsia and polyphagia were significantly reduced in Add on group compared to control group. It was observed that a majority of subjects did not require change in the dose and type of OHA that they were taking at baseline. Subjects participating in the study were already taking OHA being prescribed by their physician and the same were allowed to continue. No change in the OHA dose was made by the investigator. Also, if reduction in the dose was required the same was done in consultation with the treating physician of the subject. The criteria for reduction of dose of OHA were based on the monthly change in blood sugar levels and symptomatic assessment.

These results suggest that Yesaka liquid as add on therapy to conventional OHAs effectively helps in overall better management of diabetes. Synergism of ingredients present in Yesaka Liquid could have helped in overall better control of diabetes.

The Ingredients present in Yesaka liquid possess anti-diabetic activity.[9-14] Various in vovo and *in vitro* showed that *Gymnema sylvestre* helps to stimulate secretion or release of the insulin.[15-20] It also helps to promote regeneration of islet cells in streptozotocin-induced rat models.[21,22] *Gymnema sylvestre* assists in increasing activities of enzymes responsible for utilization of glucose by insulin-dependent pathways such as increase in phosphorylase activity and decrease in gluconeogenic enzymes and sorbitol dehydrogenase.[23] It helps in inhibition of absorption of glucose from intestine.[24] *Emblica officinalis* reduces blood glucose level by inhibition of glucose absorption and activation of β cells.[25] *Syzygium cumini* plays important role in repairing the damage of the pancreatic β cells and promoting insulin synthesis, thus lowering the level of plasma glucose.[26] *Curcuma longa* helps reduce blood sugar level and protect from long term complications of diabetes.[27] *Picrorhiza kurroa* promotes increase in the insulin mediated translocation of GLUT-4 from cytosol to plasma membrane or increase GLUT-4 expression, which in turn facilitates glucose uptake by skeletal muscles. Also, *Picrorhiza kurroa* helps in regeneration of β-cells of pancreatic islets.[28]

Yesaka was found to be safe as there was insignificant change in any of the vital parameters and laboratory investigations. One additional noteworthy finding was the effect of Yasaka on HDL cholesterol levels which showed a significant increase over a period of 90 days, implying its cardio-protective effect. The study reported a few AE in both the study groups. However, the AE were found to be not related to the study drug or procedure. Based on the above finding, it could be said that Yesaka Liquid was safe to use over a long term.

Conclusion

The study concludes that Yesaka liquid is an effective remedy as add-on therapy to OHAs which helps in the effective management of DM by helping in controlling the levels of HbA1c and Blood Sugar. Yesaka liquid is also effective in reducing symptoms of diabetes such as polyuria, polydipsia and polyphagia. Yesaka Liquid can be recommended as a safe and effective remedy for the proper management of DM. Further studies with larger sample size are required to establish efficacy of Yasaka liquid.

Acknowledgment

Authors would like to acknowledge Late Dr. G. Shrinivasa Acharya, Former Principal and Head, Dept of Kayachikitsa, SDM Ayurveda Hospital, Udupi, Karnataka, India, for conducting trial at his site.

Financial support and sponsorship

The financial support was received from Simandhar Herbals Pvt. Ltd., Mumbai for the clinical study.

Conflicts of interest

There are no conflicts of interest.

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सारांश

परिचय: यसाका लिक्विड एक प्रोपराइटरी आयुर्वेदिक योग है, जिसमें त्रिफला, जामुन, कुटकी, हरिद्रा आदि द्रव्योके घनका उपयोग किया गया है| ये वनस्पति औषधियाँ प्रमेहहर तथा एंटीऑक्सीडेंट के रूप में स्थापित है| मधुमेह के रुग्णों में आधुनिक चिकित्सापध्दति में प्रयुक्त मधुमेहहर औषधो (ORAL HYPOGLYCEMIC AGENTS) के साथ एक संयुक्तिक चिकित्सा के रूप में यसाका लिक्विड की प्रभावकारिता तथा सुरक्षितता का परीक्षण करना था| **विधियाँ**: यह अध्ययन ५ विभिन्न अध्ययनस्थलों पर उनकी नैतिकता समिती (IEC) के स्वीकृतिपश्च्यात शुरू किया गया| अध्ययन के सहभागी रुग्णोंसे सुचित सहमती प्राप्त की गई| मधुमेहग्रस्त ११२ रुग्णो को दो समूहों में बाँटा गया, एक समुहको आधुनिक चिकित्सापध्दति (OHA) में प्रयुक्त औषध दी गई तथा दूसरे समुहको आधुनिक औषधी (OHA) साथ यसाका का प्रयोग करने को कहा गया| इस चिकित्सा अभ्यास कि अवधि ९० दिनों की थी| प्रभावकारिता का मुल्यांकन करने के लिए-रक्तपरिक्षणद्वारा HbAIC, रक्तशर्करा (Blood Sugar), HOMA-IR परिक्षण, इंसुलीनकी मात्रा आदि का प्रयोग किया गया| इसके अलावा जीवन की गुणवत्ताका परीक्षण WHO-QOL नामक प्रश्नावली के द्वारा किया गया| सुरक्षितता की जांच के लिए औषधसेवनसे होनेवाले दुष्परिणाम (Adverse Reaction) तथा प्रयोगशालीय परीक्षण जैसे लिवर, किडनी, रक्तगत चरबी इत्यादि की जाँच भी की गयी| **परिणाम**: इस अध्ययन में पाया गया कि-यसाका आधुनिक चिकित्सा पध्दति में प्रयुक्त औषधोंके साथ संयुक्तरूप से देने पर मधुमेहमें अधिक प्रभावकारी है| इस मेंरक्तगत HbAIC और रक्तशर्करा को बेहतर रूप से नियंत्रण करनेका परीणाम पाया गया| इसके अलावा यसाका के प्रयोग से मधुमेह के लक्षणोपर भी बेहतर नियंत्रण एवं जीवन की गुणवत्ता में सुधार भी अधिक पाया गया| **निष्कर्ष**: मधुमेह के प्रभावी चिकित्सा के लिए यसाका लिक्विडको एक संयुक्तिक चिकित्सा के रूप में अनुमोदित किया जासकता है|