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*Original Article*

# Herb-drug Interaction: Effect of Poly-Herbal Formulation on Glibenclamide Therapy in Patients with Type-2 Diabetes Mellitus

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## ABSTRACT

**Background:** The influence of poly-herbal formulation (Mehagni) on allopathic drug like glibenclamide mainly on plasma glucose level, lipid level and pharmacokinetic parameters in patients with type-2 diabetes mellitus. **Methods and Result:** Open-label, randomized clinical study was carried out for 90 days. Around 75 patients were screened out, based on their medication subjects were divided into group A&B 39 patients were in glibenclamide-2.5 mg (Daonil®) therapy and 36 patients were in poly-herbal formulation (Mehagni-500 mg, 2 tab/thrice a day) from past 6 months. Again 39 patients of glibenclamide therapy subdivided into group A1&A2. Group A1 (20) patients reviving glibenclamide-2.5 mg and group A2 (20) for combined study (GLB-1.5 mg+Mehagni 2 tab/twice a day). Initial day the study, analyze baseline demographic and clinical characteristics and that data was compared with end of the study report, in group A2 the high density lipoproteins (HDL) significantly increased as compared to group A1, the level of low-density lipoprotein (LDL) was significantly reduced. Bio-analytical method was developed to determine the concentrations of glibenclamide in plasma and pharmacokinetic interaction of Poly-herbal formulations on GLB therapy in type-2 diabetes mellitus patients, by using a Reverse Phase Ultra-Fast Liquid Chromatography– Photo Diode Array detector (RP-UFLC). Pharmacokinetic parameters of glibenclamide in the co-administration poly-herbal formulation such as area under the curve (AUC) and mean residence time (MRT) were increased while clearance (CL) was decreased. **Conclusion:** The co-administration of poly-herbal formulation (500 mg tablet twice a day) with glibenclamide may have beneficial effect to the patients in better glycemic control, lipid-lowering effect and bioavailability.

**Key words:** Type-II diabetes mellitus, Poly-herbal formulation, Mehagni, Glibenclamide, RP-UFLC, pharmacokinetic study.

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## INTRODUCTION

Diabetes mellitus (DM) is rapidly becoming a worldwide health crisis. In 97% of DM patient's worldwide, large proportion of the individuals are pre-diabetic and 90% of thetype-2 diabetes mellitus (T2DM) patients are present across the world.[1] Now a days, T2DM consider as a life-style disease, is usually associated with urbanization, modernization, change in life style habits and food habits. The insulin resistance express at the peripheral level causes marred utilization of glucose leading to hyperglycemia, which is believed to be part in the etiology of a broad spectrum of metabolic disorders such as obesity,[2] atherosclerosis, hypertension,[3] nephropathy,[4] neuropathy,[5] retinopathy[6] and mortality.

There are varieties of hypoglycemic agents available in the market for the treatment of T2DM with differing mechanisms of action, although side effects, including hyperlipidemia and the risk of hypoglycemia, such has been the main obstacles delaying achievement of glycemic targets.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (HbA1c) determinations, to determine the minimum effective dosage and to detect primary failure (inadequate lowering of blood glucose concentrations at the maximum recommended dosage) or secondary failure (progressive deterioration in blood sugar control following an initial period of effectiveness). The rate of primary failure will vary greatly depending upon patient selection and adherence to diet and exercise.

The limitation of currently available oral anti-diabetic agents either in terms of efficacy/safety coupled with the appearance of the disease into worldwide prevalent has encouraged alternative therapy that can manage T2DM more efficiently and safely.

The Indian earliest literature, reports more than 800 herbal plant species with anti-diabetic properties.[7] Herbs are also known to provide alternative therapy in the inhibition of the diabetic complications, including cholesterol lowering action. Some of these herbs also have been confirmed to help in the re-development of β-cells and in overwhelming insulin resistance.[8]

The alternative therapies with anti-hyperglycemic effects are progressively required by pateints with diabetes. Herbs used for diabetes are likely to have the draw backs of conventional drugs, potential herb-drug interactions should be kept in mind for patients also receiving conventional anti-diabetic drugs.

The scientific data on interactions and extent of interactions make an important part of product monograph. All the product monographs and label information, detail extensively on drug-drug interactions, but it is not the same case with herb-drug interactions. The monographs do not provide adequate information to the prescriber with respect to the herb-drug interactions. The monographs of glibenclamide state that the interaction with poly-herbal products is not established. As pointed out by,[9] herb-drug interactions are under reported. There are a few case reports or case series addressing. This indicates that the scientific data collection regarding herb-drug interactions continues to be an antique part and remains as unmet need in rationalizing the use of herbal drugs as related medications.

Polypharmacy is a common phenomenon in the T2DM. In addition to the prescribed medications, patients add their own medications specially the herbal home remedies and poly-herbal formulations with or without prescriber's notice. It is known that all ingested substances have the

potential to interact.

The literature suggests that the herbal formulations drug market has witnessed exponential growth in the last decade and is getting popular not only in the developing countries, but also in the developed countries. This indicates the magnitude of usage of herbal medicines. It cannot be generalized that the herbal drugs are 'safe' and they do not cause adverse events. Many medicinal herbs, dry extracts of herbs or poly-herbal formulations may show therapeutic benefits at one dose and toxicity at another. Herbal medicines by choice or by chance, concomitantly used with the prescribed allopathic drugs, may lead to herb-drug interactions[10] causing significant variations in the pharmacokinetics and pharmaco dynamics of either drug/s, leading to increased or decreased effect or toxicity due to either component. Antagonistic interactions may render the treatment in-effective and synergistic reactions may enhance the pharmacologic response and sometimes may lead to toxicity, complicating dose, dosage regimen adjustment and individualization of therapy.

The possibility of herb-drug interactions affecting safety and efficacy of the prescribed medicines and disturbing prevalence data on diabetes, we thought of exploring the effect of herb-drug interactions and rationality of the use of herbs along with oral antidiabetic medications.

Poly-herbal formulation (Mehagni) holding curcumin, amalaki, madhunasini and ekanayakam, used as anti-diabetic drug in T2DM (Table 1). Clinical benefit of the curcumin is influencing the regulatory gene products such as COX-2; accelerate nitric oxide synthase and tumor necrosis factor which are inflammatory mediators. These mediators are plays a major role in the development of insulin resistance[11,12] Experiments on animal models have reported that curcumin has enhanced the sensitivity to insulin, decreased the body weight in obese rats and lowered the blood glucose and lipid levels in various diabetic rat models. Curcumin is a P-gp inhibitor; co-administration is known to increase the bioavailability of different P-gp substrate drugs. Little is known about the clinical benefit of the curcumin pretreatment in patients with T2DM and hyperlipidemia. Curcumin reduced LDL and VLDL levels and increased HDL levels in patients with T2DM.[13] Amalaki, which reduces thio-barbituric acid-reactive substance level significantly, it indicates the reduction in lipid peroxidation with this the serum adiponectin levels also improved significantly.[14] Adiponectin is a protein which is present in human serum it is involved in regulating glucose levels as well as a fatty acid breakdown. Madhunashni (gymnemic acid) it delays the absorption of glucose in the blood. The atomic arrangement of gymnemic acid molecules is just like to that of glucose molecules. Checking the sugar craving, similar gymnemic acid molecules attached to the receptor location in the hygroscopic external layers of the intestine, thereby preventing the sugar molecule absorption by the intestine which results in reducing the glucose level.[15] Ekanayakam (Salacia Oblonga) herb contains α-Glucosidase inhibitors Salacinol and Kotalanol these two inhibitors help in regulating glucose levels in the body.[16] All these elements of poly-herbal formulation can give a good influence on T2DM complications. Though the commercially available poly-herbal formulation is utilized by the patients with DM as an alternative therapy, its interaction with widely used anti-diabetic drugs is not yet evaluated. The present analysis was carried out with an idea that, poly-herbal formulation might impact on the blood glucose level, lipid level and pharmacokinetic (PK) parameters of oral anti-diabetic drug (Glibenclamide). For analyzing the pharmacokinetic parameters of oral anti-diabetic drug using a developed and validated bio-analytical method by ultra-fast liquid chromatography. The main objective of the present study is to estimation of therapeutic benefits of this combination in diabetic patients.

# MATERIALS AND METHODS

### *Materials*

Glibenclamide (GLB) was obtained as a gift sample from Wockhardt Pharma Pvt. Ltd. Aurangabad, Maharashtra, India. Mehagni poly-herbal formulation (500 mg) was provided by SNA Oushadhasala Pvt. Ltd. Kerala, India. Lipid estimation kits were purchased from Merck, Bangalore, India. Methanol, acetonitrile and other solvents used for the high-performance liquid chromatography (HPLC) were of HPLC grade. All other chemicals and reagents used in this study were of analytical grade.

### *Ethical clearance*

The study proposal was approved by Institutional Human Ethical Committee of JSS Ayurveda medical hospital, Mysuru, Karnataka, India. (Proposal no.08/2014, Ref. No. JSSAMC/352/2014-2015). The written consent was taken from each patients before starting the study and each patient has given freedom to drop out from the study at any time without giving any reason.

## Study design

### *Selection of cases*

Under the guidance of physicians, 96 patients were selected as showed in flow chart (Figure 1) and open label randomized clinical study was conducted at JSS Ayurveda Medical Hospital, Lalithadripuram, Mysuru, Karnataka, India. The selected patients were subjected to general medical checkup with code numbers and asked to present themselves on a specified date for sample collection. Instructions related to maintenance of diet were given to the patients.

### *Inclusion Criteria*

- Patients of either sex (male or female)
- Age-35 to 65 years
- T2DM patients with fasting plasma glucose level equal to or greater than 140 mg/dl of blood
- Without any detectable /visible secondary diabetic complications
- T2DM patients with a history of inadequate control of blood glucose levels with oral hypoglycemic agents

### *Exclusion Criteria*

- Pregnant or nursing patients
- Smokers
- Patients with any secondary diabetic complication
- Patients suffering from Type-1 diabetes mellitus (T1DM)

### *Intervention & adherence*

Patient enrolled in the study provided written informed consent after receiving oral and written explanation of the study. Total of 96 patients were screened based on their case history. On the basis of exclusion criteria 21 patients were excluded from the study. The remaining 75 patients were divided into two groups; group A (39 patients) with the glibenclamide therapy (2.5 mg tablet/day) and group B (36 patients) taking the poly-herbal formulation (mehagni-500 mg, 2 tablets thrice a day) from last six months. Baseline demographics and clinical characteristics were assessed in all patients. Group A patients were further subdivided into two groups; Group A1 (20 patients) with the continuation of glibenclamide therapy and Group A2 (19 patients) receives combined therapy (Glibenclamide (1 mg tablet/day) + mehagni-500 mg (2 tablets twice a day). The specific instructions regarding dietary and life style modification were provided by the study coordinator to patients.

### *Outcome assessment*

The *Anthropometric parameters* for this research were body weight and body mass index. The *Metabolic parameters* includes FBS, PPBS, and HbA1c, lipid levels including TG, T-Chol, HDL and LDL. Both *Anthropometric* & *Metabolic parameters* were measured at baseline, 2nd, 4th, 6th & 12th week time points. The pharmacokinetic parameters of glibenclamide were assessed at the end of the study using RP-UFLC (Shimadzu 1100 series).

### *Safety measures*

Safety was monitored by closely assessing patients reported symptoms (nausea, vomiting), changes in *Anthropometric parameters*, vital signs, laboratory tests (complete blood count, plasma creatinine, blood urea nitrogen and liver function tests), and reports of hypoglycemia during the study period. Patients were advised to record all adverse events in diary provided during the study. If they had any abnormal events, they were instructed to visit to hospital before the next appointment. *Collection of blood samples.*

Blood samples (2 ml) were collected from the patients at the start of the study and were checked for all metabolic parameters.

Following the administration of combine therapy blood samples (2 mL) were collected from the patients at baseline, 2nd, 4th, 6th & 12th week time points. During treatment period, patients received both poly-herbal tablet and allopathic drug. The blood samples were collected for pharmacokinetic study at 0, 0.5, 1, 2, 3, 4, 6, 8 and 12 hr of 90th day. The blood samples were allowed to clot for 10 min at room temperature and were centrifuged at 10,000 rpm for 10 min to obtain the serum. Estimation of glucose and lipids were carried out immediately, and the remaining samples were stored at -20°C until UFLC analysis.

### *Quantitative Determination of Plasma Glucose Level and Lipid Levels*

The estimation of plasma glucose level was done by glucose oxidase (GOD) and peroxidase (POD) method.[17] The plasma lipid level was estimated by using a lipid kit (Merck, Bangalore, India) and a semi-autoanalyser in laboratory of JSS Ayurveda College and Hospital, lalithadripuram, Mysuru, Karnataka, India.HbA1c were analyzed by using BIO_RAD D-10™ dual program systembased on principle of ion-exchange high-performance liquid chromatography.[18] Average reading were taken by analyzing each sample in triplicates (n=3).

### *Method developed by using Ultra-Fast Liquid Chromatography (UFLC)*

The bio-analytical method was developed by using UFLC (Ultra-Fast liquid chromatograph Shimadzu 1100 series) for quantification of glibenclamide in patient's plasma by using glipizide as an internal standard (IS) with optimized chromatographic condition. Plasma sample was extracted using protein precipitation method.[19] The chromatography separation was achieved with kinetex $C_{18}$ column (250 X 4.60 mm, 100 A, 5 µ) with mobile phase containing Acetonitrile & 0.01N sodium dihydrogen orthophosphate (pH- 3.5 adjusted with orthophoshoric acid) in 60:40 ratio with gradient mode. The flow rate was 1 mL/min maintained at 40°C and the injection volume was 10 µl. Total run time was set for 10 min and chromatograms were recorded at 254 nm.

### *Method validation*

The bio-analytical method had been validated according to USFDA-guidelines.[19] Samples of blank plasma, Plasma spiked with the glibenclamide and internal standard followed by centrifugation were used to evaluate the specificity. Calibration curves were described in the form of y=mx+c by plotting the peak area of the anayte *verses* concentration. The lower limit of quantification (LLOQ) was defined as the lowest quantifiable concentration of the standard curve (LOQ, S/N=10). The limit of detection (LOD) was defined as the detectable amount (LOD, S/N=3).

The intra and interday precision was defined as the relative standard deviation (RSD), and the accuracy was assessed by comparing the measured concentration with its true value.

The accuracy and precision were assessed by determining QC samples at three different validation batches. The intrabatch QC sample were prepared for six replicates. The acceptable intra and interday precision should be less than within 15% for all QC samples.

The matrix effect at three QC concentration was assayed in sets of six replicates. The extraction recoveries of analytes at three QC levels were evaluated by determining the peak area ratios of the analytes in the post-extraction spiked samples to that acquired from pre-extraction spiked samples. The matrix effects were studied by comparing the peak areas of the analytes dissolved in the pretreated blank plasma with that of pure standard solution containing equivalent amounts of the analytes. The matrix effect was implied if the ratio was less than 85% or more than 115%.

Stability of the analytes in human plasma was assessed by analyzing five replicates of QC samples at three concentrations stored for 4 hr at room temperature, three cycles of freezing at −20°C and thawing and stored for 20 days at −20°C, respectively. The extracted QC samples kept in the auto-sampler at 4°C for 12 hr were analyzed to evaluate post-preparation stability.

### *Pharmacokinetic analysis*

Pharmacokinetic analysis was achieved by a non-compartmental approach[20] The area under the concentration *versus* time curve (AUC) was calculated by trapezoidal rule from zero to the last measured concentration.[21] The average time for the residence of all the drug molecules in the body which was called mean residence time (MRT) was calculated. The pharmacokinetic parameters (Table 4), such as maximum plasma concentration ($C_{max}$) and time of maximum concentration ($T_{max}$), were directly obtained from the plasma concentration *versus* time plots. The elimination rate constants ($K_e$) were determined by the linear regression analysis of the logarithmic transformation of the last four data points of the curve The area under the concentration *versus* time curve from zero to infinity ($AUC_{0-\infty}$), total clearance (CL), and the volume of distribution ($V_d$) of drug were calculated. '*C*' is the drug concentration in plasma, '*CL*' is the total body clearance of the drug from the plasma, and $C_p$ is the drug blood concentration at time zero. Initial drug concentration was calculated from the best fitted line and is back extrapolated to the y-axis. The y-intercept was taken as an initial drug concentration ($C_p$). The values were calculated by Microsoft Excel the pharmacokinetic parameters were expressed as the mean ± S.D (Standard deviation).

### *Statistical analysis*

All the data were expressed as mean ± standard deviation. The statically evaluated data were done by independent student *t*-tests to examine the differences in baseline demographic and clinical characteristics and after treatment performed to determine the changes in anthropometric measurement and metabolic parameters in the poly-herbal formulation and allopathic formulations groups within the 3 months of period. The significant changes from baseline to after treatment within groups were tested with paired *t*-tests. The unpaired t-test was applied for comparison between the 2 groups, the significant value was set as $P<0.05$ and the pharmacokinetic parameters were calculated by PK solution software and IBM SPSS version 20.0 software.

## RESULTS

### *Development and Optimization of Chromatographic Conditions*

Optimization of the chromatographic conditions are proposed to take into consider the several aims of method development and to assess each

goal (resolution, runtime, sensitivity, peak symmetry, etc.) accurately, according to the requirement of UFLC method being used for the estimation of drug in patients plasma. The glibenclamide is not totally soluble in water whereas soluble in organic solvents like methanol and acetonitrile. During the development phase, the mobile phase containing methanol and buffer (pH-4) resulted in high run time, retention time shift to more than 7 min, asymmetric peaks with poor resolution and greater tailing factor (>2). The successful use of mobile phase for glibenclamide mobile phase containing mixture of acetonitrile and 0.01N 0.01N sodium dihydrogen orthophosphate (pH-3.5 adjusted with orthophoshoric acid) in the ratio of 60:40 v/v fixed at the flowrate 1 mL/min reduced tailing (<1.5) and resulted in goodpeak symmetry and resolution (>1.5) The glibenclamide were monitored at 254 nm, the retention times 4.4 min IS was eluted at 3.7 min (Figure 2).

### *Validation of the Developed Method*
### *Linearity and Calibration Curve.*

The linearity was tested at the concentration range of 200–1000 ng/mL and the calibration curve constructed was evaluated by its correlation coefficient. The correlation coefficient (*r*) for all the calibration curves was consistently greater than 0.9983 ± 0.0003 (Figure 3).

### *Method Sensitivity and Specificity*

The 10 min LC run, the glibenclamide at 200 ng/mL investigation could be easily detected from human plasma matrices (*n*=6). Confirmation of glibenclamide could be readily achieved by comparing the retention time obtained from the sample with their standard drug. The lower limit of quantification (LLOQ) was defined as the lower concentration that could consistently produce accurate and precise chromatogram that could be quantified. Shows the chromatogram of the drugs obtained from plasma and samples spiked with the concentration at LLOQ. All the chromatograms were analyzed and glibenclamide peaks did not interfere with any endogenous components.

### *Accuracy, Precision and Recovery*

For determining the accuracy of the proposed method, different quality control (QC) levels of drug concentrations in plasma [lower quality control samples (LQC) 600 ng/ml, medium quality control samples (MQC) 800 ng/ml, and higher quality control samples (HQC) 1000 ng/ml were prepared independently and analyzed.

Both repeatability (inter-day precision) and reproducibility (intra-day precision) were determined as follows (Table 2). Solutions containing low, intermediate and highest quantification concentrations (LQC, MQC and HQC) of the calibration curve, i.e. 600 ng/ml, 800 ng/ml, 1000 ng/ml was prepared. Six injections at each of the specified concentration levels were injected within the same day for repeatability, and over a period of 3 days (6 injections/day) for reproducibility. The mean and relative standard deviation were calculated and used to judge the accuracy and precision of the method. The precision for all these analytes under investigation did not exceed 15% at any of the concentrations studied and well met the requirements of validation.

### *Stability*

The stability of samples reconstituted after extraction from plasma was investigated under various storage conditions. Short-term stability was studied at room temperature for 8 hr, long-term stability studies were done at -20°C for 30days, auto-sampler done for 24 hours and freeze-thaw stability study was also evaluated by successive cycles of freezing and thawing the samples by storing at -20°C and room temperature, respectively. Three complete freeze thaw cycles were performed. They were carried out at 2% stability was estimated by comparing the mean of back calculated concentrations of all analytes from the stored stability samples with that of freshly spiked QC samples. The results indicated that each analyte had an acceptable stability under those conditions, as shown in (Table 3).

### *Recovery of Drugs from Plasma*

Protein precipitation method was found to be successful in extraction of glibenclamide and glipizide (IS) drug from human plasma and the recovery was determined by comparing peak areas of spiked plasma extracts with their standard freshly prepared in acetonitrile. Plasma samples (*n*=5) spiked with the analytes at their respective LLOQ, LQC, MQC and HQC levels were analyzed. The area ratios of the targeted drugs were compared with those obtained from blank extracts spiked with the target drug after extraction (taken as 100% recovery of the drug from that particular matrix). Recoveries of the drugs are summarized in (Table 4).

### *Demographic and clinical characteristics*

The base line demographic and clinical characteristics of the study were presented in (Table 5). Overall, glibenclamide therapy and poly-herbal formulation therapy participants consisted of mean age, height, body weight, body mass index (BMI), fasting blood glucose level, postperidonial blood glucose (PPBS), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (T-Chol), , high density lipoprotein (HDL), and low density lipoprotein (LDL). There were no significant difference in demographic characteristics between the 2 groups.

### *Metabolic parameters*

Overall, the preliminary study was showed that significantly decreased in FBS, PPBS and HbA1c compared to baseline demographic and clinical values in Group A1 compared to Group A2 ($P$<0.01, $P$<0.04, $P$<0.03) (Table 6).

### *Analysis of pharmacokinetic parameters*

The mean plasma concentration–time curves for subjects of group A1 and A2 are presented in (Figure 4) shows the curves for glibenclamide (2.5 mg) after oral administration of glibenclamide alone and co-administration with poly-herbal formulation. It can be observed that first an increase of the concentration of glibenclamide, when it's in combination compared to alone at each 0.5, 1, 2, 3, 4, 6, 8 &12 hr (Table 7). The mean pharmacokinetic parameters of glibenclamide alone and its combination with poly-herbal formulation were given in (Table 8). $C_{max}$ of glibenclamide when it's in combination at the second hour were increased significantly, compared to when it's in alone treatment 189.0 ± 51.69 (p <0.05). Area under curve were altered significantly. When treated with glibenclamide alone, $AUC_{0\_t}$ $AUC_{0\_\infty}$ and $MRT_{0\_\infty}$ were 912.3 ± 86.34, 1035 ± 23.65 and 6.356 ± 0.231. Co-administration of glibenclamide and poly-herbal formulation, $AUC_{0\_t}$ $AUC_{0_\infty}$and $MRT_{0\_\infty}$ of glibenclamide were significantly increased by 1456 ± 56.32, 1836 ± 25.32 and 7.893 ± 26.35, $p$<0.05 respectively, while Cl/F was significantly decreased by 47.2%. These results showed that the pharmacokinetics of glibenclamide changed when being co-administered.

## DISCUSSION

There are some evidence for poly-herbal formulation which are available in market to maintain diabetic condition prescribe by physicians for example Diabecon, Dia-Care, Diabetes- Daily Care, DIABETA etc. from different manufacturing companies.[22] These formulations contains more than two active ingredients which are more active against to diabetes and reported that increase peripheral utilization of glucose, hepatic and muscle glucagon contents, promotes β-cells repair and regeneration, it has antioxidant properties and protect β cells from oxidative stress and anti-hyperlipidemias, anti-stress. Poly-herbal formulations act on different sites in differing ways to effectively control factors and pathways leading to diabetes mellitus. In the case of group A1 TG, T-Chol, LDL

**Table 1: Composition of Poly-herbal formulation Mehagni-500mg tablet Each 100 mg contains**

| Ingredient | Botanical name | Family | Quantity |
|---|---|---|---|
| **Curcumin** | Curcuma longa L | Zingberaceae | 20 mg |
| **Amalaki** | Emblica Officinalis | Euphorbiaceae | 20 mg |
| **Madhunashini** | Gymnema Sylvestre | Asclepiadaceae | 30 mg |
| **Ekanayakam** | Salacia Reticulata | celastraceae | 30 mg |

**Table 2: Intra-day and Inter-day precision data of GLB**

| QC ID | QC Sample (ng/ml) | Intra-day | | | Inter-day | | |
|---|---|---|---|---|---|---|---|
| | | Found Mean conc (ng/ml) ± SD (n=6) | RSD % | Acuracy % | Found Mean conc (ng/ml) ± SD (n=6) | RSD % | Acuracy % |
| **LQC** | 600 | 660.83 ± 62.95 | 5.05 | 109.47 | 648.13 ± 4.83 | 6.58 | 108.86 |
| **MQC** | 800 | 843.12 ± 39.08 | 4.36 | 108.89 | 855.6 ± 47.79 | 5.90 | 105.76 |
| **HQC** | 1000 | 1176.3 ± 41.0 | 3.68 | 114.63 | 1168.7 ± 54.28 | 3.23 | 106.86 |

SD: standard deviation, RSD (%): relative standard deviation= (SD x 100/mean)

Accuracy (%) = (Found mean concentration – nominal concentration)/ (nominal concentration) x100

**Table 3: Stability of GLB in human plasma during storage and sample handling**

| Stability | QC sample (ng/ ml) | Mean ± SD (n=5) (ng /ml) | Accuracy (%) | RSD (%) |
|---|---|---|---|---|
| **Long-term(30days)** | 600 | 648.4 ± 40.15 | 110.70 | 6.50 |
| | 800 | 836.6 ± 34.34 | 105.45 | 5.17 |
| | 1000 | 1084.6 ± 66.3 | 109.86 | 6.02 |
| **Short-term(8 hours)** | 600 | 650.4 ± 41.1 | 111.07 | 4.72 |
| | 800 | 841.2 ± 37.63 | 109.87 | 4.74 |
| | 1000 | 1079 ± 38.84 | 107.9 | 4.16 |
| **Auto-sampler(24 hours)** | 600 | 655.6 ± 30.98 | 111.93 | 5.60 |
| | 800 | 882.1 ± 46.91 | 108.75 | 5.21 |
| | 1000 | 1087 ± 38.28 | 109.76 | 4.55 |
| **Freeze-Thaw** | 600 | 668.4 ± 44.56 | 108.73 | 5.76 |
| | 800 | 871 ± 47.04 | 106.12 | 5.59 |
| | 1000 | 1095 ± 37.33 | 106.5 | 4.47 |

SD: standard deviation, RSD (%): relative standard deviation= (SD x 100/mean)

**Table 4: Extraction recovery (ER) and matrix effect (ME) of GLB and GLP (IS) (n=5)**

| Analytes | QC sample (ng/ml) | RSD (%) | ER (%) | ME (%) |
|---|---|---|---|---|
| **GLB** | 600 | 4.38 | 110.66 | 99.46 |
| | 800 | 4.98 | 107.12 | 100.12 |
| | 1000 | 6.53 | 109.45 | 101.45 |
| **GLP(IS)** | 400 | 3.24 | 109.56 | 109.96 |

RSD (%): Relative standard deviation= (SD x 100/mean).

ME (%): (Analyte peak area of extracted plasma residue / analyte peak area of neat solution) x 100

ER- Extraction recovery

**Table 5: Baseline demographics and clinical characteristic**

| | GLB (2.5 mg) (n=20) | GLB (1.5 mg)+Mehagni (n=20) |
|---|---|---|
| **Age (years)** | 46.60 ± 2.63 | 40.10 ± 1.663 |
| **Height (cm)** | 160.20 ± 12.63 | 174.55 ± 12.382 |
| **Weight (kg)** | 74.40 ± 8.771 | 74.21 ± 2.840 |
| **BMI (kg/m2)** | 29.83 ± 10.523 | 33.90 ± 2.918 |
| **FBS (mg/dl)** | 162.70 ± 18.282 | 149.85 ± 16.693 |
| **PPBS (mg/dl)** | 257.56 ± 61.76 | 231.84 ± 53.469 |
| **HbA1c (%)** | 9.15 ± 2.048 | 9.74 ± 1.743 |
| **T G (mg/dl)** | 156.20 ± 9.138 | 160.40 ± 5.374 |
| **T-Chol (mg/dl)** | 171.80 ± 8.417 | 174.05 ± 4.143 |
| **HDL (mg/dl)** | 31.00 ± 3.606 | 45.35 ± 4.295 |
| **LDL (mg/dl)** | 121.30 ± 9.569 | 121.80 ± 5.238 |

BMI, body mass index; FBS, fasting blood glucose; PPBS, postperidonial blood glucose; HbA1c, Glycated hemoglobin; TG, triglycerides; T-Chol, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein.

and HDL level doesn't change as compared to baseline (Prasad Neerati, *et.al.* 2014.). But in combined study increasing HDL level significantly and decreasing TG, T-Chol and LDL significantly ($P$<0.05). Based on literature and clinical data evidence shows poly herbal formulation is combo pack it can be significantly decrease the blood glucose level and blood lipid levels. But glibenclamide only decreasing blood glucose level

**Table 6: Body composition and chemistry biomarker measures after treatment**

| | Baseline | 2nd week | 4th week | 6th week | 8th week | 12th week |
|---|---|---|---|---|---|---|
| **GLB group (2.5 mg)** | | | | | | |
| **Weight (kg)** | 79.27 ± 5.49 | 79.57 ± 4.49 | 79.57 ± 4.49 | 79.28 ± 3.49 | 79.28 ± 3.49 | 80.14 ± 6.479 |
| **BMI (kg/m2)** | 33.28 ± 2.87 | 33.25 ± 3.87 | 33.25 ± 3.87 | 32.21 ± 2.77 | 32.21 ± 2.77 | 32.02 ± 1.830 |
| **FBS (mg/dl)** | 147.0 ± 15.3 | 149.0 ± 15.2 | 149.0 ± 15.2 | 154.0 ± 25.4 | 154.0 ± 25.4 | 149.850 ± 3.559 |
| **PPBS (mg/dl)** | 213.58 ± 29.89 | 215.68 ± 19.89 | 215.68 ± 19.89 | 212.58 ± 22.89 | 212.58 ± 22.89 | 215.55 ± 15.559 |
| **HbA1c (%)** | 9.20 ± 1.067 | 9.05 ± 1.067 | 9.05 ± 1.067 | 9.09 ± 1.067 | 9.09 ± 1.067 | 9.62 ± 0.521 |
| **T G (mg/dl)** | 165.55 ± 3.83 | 165.55 ± 3.83 | 165.55 ± 3.83 | 165.55 ± 3.830 | 165.55 ± 3.830 | 160.73 ± 4.982 |
| **T-Chol (mg/dl)** | 166.14 ± 2.7 | 165.62 ± 2.5 | 165.62 ± 2.5 | 164.64 ± 2.6 | 164.64 ± 2.6 | 166.18 ± 9.908 |
| **HDL-C (mg/dl)** | 45.09 ± 6.58 | 45.09 ± 6.580 | 45.09 ± 6.580 | 45.09 ± 6.580 | 45.09 ± 6.580 | 43.89 ± 9.780 |
| **LDL-C (mg/dl)** | 117.18 ± 4.55 | 117.18 ± 4.557 | 117.18 ± 4.557 | 117.18 ± 4.557 | 117.18 ± 4.557 | 118.30 ± 4.554 |
| **GLB 1.5 mg+Mehagni group (2 tablet/twice a day)** | | | | | | |
| **Weight (kg)** | 74.21 ± 2.840 | 73.21 ± 3.840 | 73.21 ± 3.840 | 72.23 ± 2.840 | 72.23 ± 2.840 | 72.11 ± 2.320 |
| **BMI (kg/m2)** | 33.90 ± 2.918 | 33.40 ± 2.18 | 33.40 ± 2.18 | 32.40 ± 2.98 | 32.40 ± 2.98 | 32.23 ± 1.22 |
| **FBS (mg/dl)** | 149.85 ± 16.693 | 143.15 ± 16.03 | 143.15 ± 16.03 | 141.45 ± 26.63 | 141.45 ± 26.63 | 135.85 ± 3.84 |
| **PPBS (mg/dl)** | 231.84 ± 53.469 | 228.24 ± 23.469 | 228.24 ± 23.469 | 196.66 ± 53.469 | 196.66 ± 53.469 | 153.37 ± 14.384 |
| **HbA1c (%)** | 9.74 ± 1.743 | 9.24 ± 1.43 | 9.24 ± 1.43 | 8.74 ± 1.74 | 8.74 ± 1.74 | 7.38 ± 0.980 |
| **T G (mg/dl)** | 160.40 ± 5.374 | 150.40 ± 4.74 | 150.40 ± 4.74 | 130.40 ± 4.34 | 130.40 ± 4.34 | 128.45 ± 13.851 |
| **T-Chol (mg/dl)** | 174.05 ± 4.143 | 170.12 ± 4.13 | 170.12 ± 4.13 | 154.45 ± 3.143 | 154.45 ± 3.143 | 138.80 ± 9.704 |
| **HDL-C (mg/dl)** | 31.35 ± 4.295 | 31.12 ± 1.295 | 31.12 ± 1.295 | 32.35 ± 4.295 | 32.35 ± 4.295 | 36.40 ± 1.453 |
| **LDL-C (mg/dl)** | 121.80 ± 5.238 | 119.50 ± 4.38 | 119.50 ± 4.38 | 111.40 ± 5.238 | 111.40 ± 5.238 | 107.55 ± 2.412 |

BMI, body mass index; FBS, fasting blood glucose; PPBS, postperidonial blood glucose; HbA1c, Glycated hemoglobin; TG, triglycerides; T-Chol, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein. Data are expressed as mean ± SD, and number with percentage in parenthesis.

**Table 7: Mean changes in plasma glibenclamide concentration (in nano gram per milliliter), with and without Mehagni (poly-herbal formulation)**

| Time (h) | GLB (mean ± SD) | GLB + Mehagni (mean ± SD) |
|---|---|---|
| **0** | 0 ± 0 | 0 ± 0 |
| **0.5** | 96.12 ± 21.29 | 107.12 ± 14.29 |
| **1** | 116.50 ± 35.43 | 129.09 ± 35.43 |
| **2** | 183.37 ± 61.27 | 190.37 ± 61.27 |
| **3** | 190.62 ± 56.75 | 219.62 ± 56.75 |
| **4** | 169.50 ± 51.69 | 179.05 ± 51.69 |
| **6** | 137.50 ± 42.59 | 143.12 ± 42.59 |
| **8** | 106.50 ± 19.73 | 116.04 ± 29.13 |
| **12** | 90.87 ± 7.56 | 101.875 ± 5.16 |

Values are expressed as mean ± standard error of mean. * Significant at $P< 0.05$.

**Table 8: Mean Pharmacokinetic parameters of glibenclamide found in with and without Mehagni (poly herbal formulation) in type-2 diabetic patients**

| Parameter | GLB | GLB+Mehagni |
|---|---|---|
| Cmax (µg/ml) | 190 ± 56.75 | 219 ± 53.62 |
| Tmax(h) | 3.6 ± 0.11 | 3.4 ± 23.12 |
| Ke (1/h) | 0.013 ± 0.020 | 0.008 ± 0.001 |
| AUC(0-12h)(µg h/ml) | 912.3 ± 86.34 | 1456 ± 56.32 |
| AUC(0-∞)(µg h/ml) | 1035 ± 23.65 | 1836 ± 25.32 |
| t1/2 (h) | 4.2 ± 0.312 | 4.531 ± 45.62 |
| MRT(0-∞) (h) | 6.356 ± 0.231 | 7.893 ± 26.35 |
| Cl/F (L/(h kg)) | 0.0023 ± 0.003 | 0.0011 ± 0.001 |
| Vd/F(L/kg) | 0.034 ± 0.002 | 0.012 ± 0.012 |

Values are expressed as mean ± standard error of mean. * Significant at $P< 0.05$.

but not lipid level so these both formulation need combination to maintain diabetic condition.

Based on these report evidence, may be in drug–drug interactions, drug–herb interactions mediated by physicochemical properties, pharmacokinetic properties and pharmacodynamics properties. Among them, pharmacokinetic properties are the main cause. Pharmacokinetic interaction between herbal medicines and drug may occur in the phase of absorption, distribution, metabolism or excretion. For most orally-administered drugs, liver is the primary site of metabolism and cytochrome P450s (CYP450) are very important drug-metabolizing enzymes. Herbal medicines that modulate intestinal and hepatic cytochromes (CYPs) can alter the bioavailability and clearance of co-administered drugs. (P. R. Sakunthala Devi *et al*., 2015). Besides, OATP1B1 (organic anion transporting polypeptides), P-glycoprotein (P-gp), BCRP (ATP Binding Cassette Protein G2 /ABCG2).[23] are well-known drug transporters, plays an important role in the absorption, distribution, or excretion of drugs, and it's can also be induced or inhibited resulting in the interactions based on transports.[24]

From our results, increase in AUC, MRT and decrease in Cl/F of glibenclamide were observed in presence of poly-herbal formulation. These

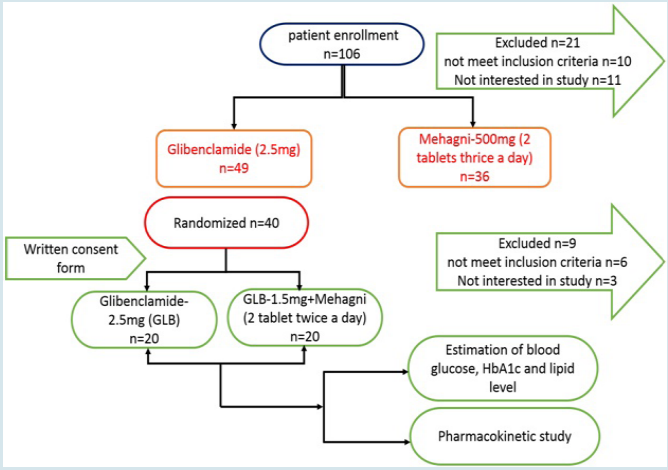


**Figure 1:** Flow chart.

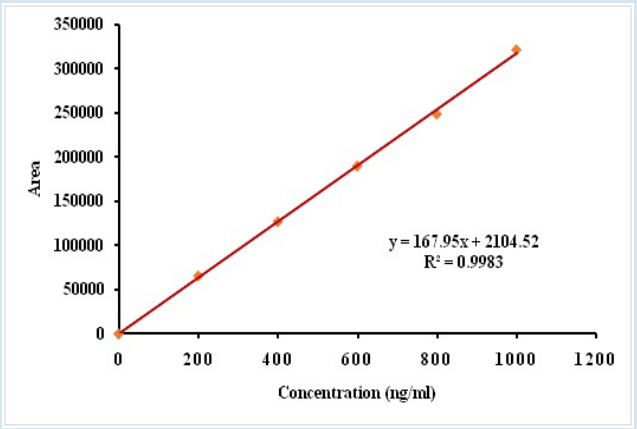


**Figure 3:** Standard calibration graph of glibenclamide.

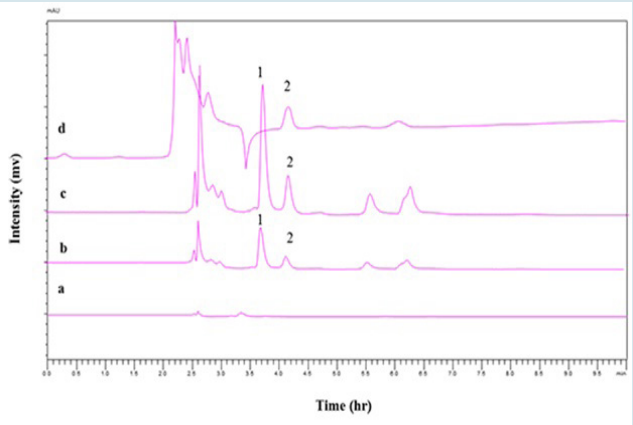


**Figure 2:** chromatograms of plasma samples.

Blank human plasma (a), Blank human plasma spiked pure sample with 500 ng/ml – GLB (b), LLOQ of pure plasma sample with 200 ng/ml – GLB (c), diabetic patient blood sample (d), Peaks: 1, Glipizide (IS) and 2, GLB.

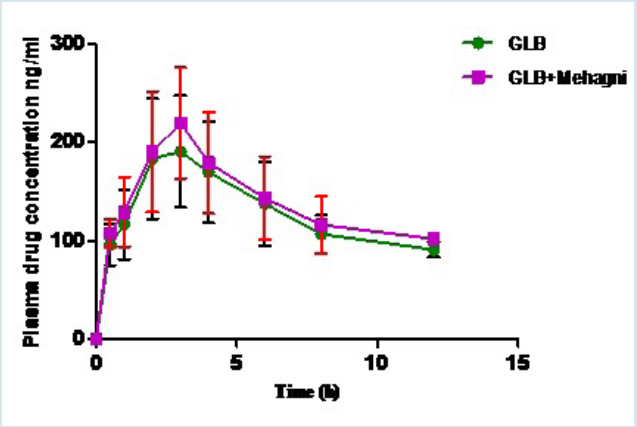


**Figure 4:** Mean plasma drug concentration (In nanogram per millilitre) of glibenclamide versus time (in hours) in typ-2 diabetic patients, with and without poly-herbal formulation treatment..

facts clearly indicated that poly-herbal formulation slowed down the metabolism of glibenclamide. At same time glibenclamide is metabolized by CYP2C9[25] and is a substrate for OATP2B1, P-gp.[26] Pharmacokinetic interactions of *curcumin* with glibenclamide, which is metabolized by CYP3A4 microsomal liver enzymes. Glibenclamide is metabolized by CYP3A4 and is a substrate for intestinal P-glycoprotein.[27] *Curcumin* could also give rise to drug interactions as it has been reported to inhibit both the function and expression of P-gp (Prasad Neerati. *et al*., 2014). Several *in-vitro* studies reported the inhibition of CYP450s, especially CYP3A4, CYP1A2, and CYP2C9 by curcumin.[28] For glibenclamide, increase in Cmax, AUC and decrease in Cl/F and V/F were observed in presence of poly-herbal formulation. These facts indicated that of poly-herbal formulation accelerated the absorption of glibenclamide and also amalaki is worthwhile to inhibition of *glutathione S-transferase* (GST) activity, because this enzyme acts as powerful drug metabolizing enzyme by its conjugation reactions with glutathione. Inhibition activity offers a possibility of combining amalaki with drugs to enhance their potential in case of drug resistance or reduction of dose.

The blood glucose levels were altered significantly, based on that poly-herbal formulation indicating potential antidiabetic activity. In reduction of plasma blood glucose levels by poly-herbal formulation treatment was believed, because whether curcumin nullified glucose transporter 2 (GLUT2) membrane translocation via inhibition of p38 MAPK signaling, and reduced GLUT2 expression by activation of PPAR-γ denovo glutathione synthesis,[29] or *Amalki* reduce blood sugar levels.[30] *Madhunashin (gymmnema sylvester)* also increasing the endogenous insulin production or by increasing the serum C-peptide levels. C-peptide is a chain of amino acids that is cleaved from the proinsulin molecule released by the pancreas to form insulin. Therefore, C-peptide is used as a marker to monitor the release of endogenous insulin and *Ekanayakam* (Salacia Oblongata) herb contains α-Glucosidase inhibitors Salacinol and Kotalanol these two inhibitors help in controlling glucose levels in the body. One of the effective managements of diabetes mellitus, in particular, type-2 diabetic mellitus to decrease postprandial hyperglycemia, is to retard the absorption of glucose by inhibition of carbohydrate hydrolyzing enzymes, such as α-glucosidase and α-amylase, in the digestive organs. α- Glucosidase is the key enzyme catalyzing the final step in the digestive process of carbohydrates. Hence, α-Glucosidase inhibitors can retard the liberation of d-glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppression of postprandial hyperglycemia.[31]

The possible mechanism of modulating anti-lipid effect by bioactive

components like *curcumin* and *Madhunashin* which are present in poly herbal formulation, were mainly responsible for the potential effect include the selective inhibition of 11β-HSD1, decrease absorption of cholesterol, and increase in the activity of cholesterol-7α-hydroxylase.[32] *Madhunashin* showed significant decrease in the total cholesterol and triglyceride levels. It also increased the HDL level and was successful in suppressing the LDL levels.[33] Gymnnema may inhibit the absorption of oleic acid, which is one of the omega-9 fatty acids found in vegetable oil, animal fat, and other sources of dietary fat.[32] Might be reduced by cholesterol synthesis in the liver or inhibition of cholesterol absorption from the intestine.

## CONCLUSION

**1st schedule**: The blood glucose level and blood lipid levels in diabetic patients were observed on the basis of patient reports, after administration of Allopathic (Glibenclamide) and glibenclamide with poly-herbal formulation (Mehagni) in groups $A_1$& $A_2$, as mentioned above. The 3 months recorded data of FBS, PPBS, HdA1c, TG, T-Chol, LDL, HDL level in diabetic patients consuming glibenclamide (Group A1) was compared to group A2 shows significantly decreasing blood glucose level & lipids level. Based on statistical study evidence shows combination of allopathic and poly-herbal formulation is a better control over on diabetic complications and may be an alternative medication for T2DM.

**2nd schedule:** The pharmacokinetic results showed that poly-herbal formulation were influenced glibenclamide when being co-administered and increased bioavailability of glibenclamide. Poly-herbal formulation could be useful for the diabetic patients on glibenclamide therapy, to obtain a better control over the blood glucose and lipid levels.

Diabetes mellitus and hyperlipidemia are the two risks that go in parallel to each other. This would become an additional advantage to the diabetic patients, who take poly-herbal formulation as an adjuvant therapy. It is giving an insight into these herbal molecules as future potential drug molecules. As the study was conducted on small sample size, additional long-term studies, with different doses of poly-herbal formulation on a large number of patients, are recommended to correlate the results of the present study. The drug–herb interaction studies are of great importance for the sake of public health. More and systematic studies are needed to investigate the mechanism of interaction.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

Author declare no conflicts of interest for the content of this article.

## ABBREVIATION USED

**AUC:** Area under curve; **BMI:** Body mass index; **CL/F:** Clearance/Fluid; **Cmax:** Maximum concentration; **C:** Drug concentration in plasma; **Cp:** drug concentration in blood at time zero; **CYP:** Cytochrome; **COX-2:** Cyclooxygenase; **DM:** Diabetes mellitus; **ER:** Extraction recovery; **FBS:** Fasting blood sugar level; **Ke:** Elimination rate constant; **IS:** Internal standard; **JSS:** Jagadguru shivarathreshwar; **JSSAMC:** JSS Ayurveda medical hospital; **GLP:** Glipizide; **GLB:** Glibenclamide; **GOD:** Glucose oxidase; **GST:** Glutathione S-transferase; **GLUT2:** Glucose transporter; **HQC:** High Quantity control; **11?-HSD:** 11?-Hydroxysteroid dehydrogenase; **HbA1C:** Glycosylated hemoglobin; **HPLC:** High performance liquid chromatography; **HDL:** High density lipid; **LDL:** Low density lipid; **LLOQ:** Lower limit of quantification; **LQC:** Low quantity control; **MRT:** Mean residence time; **ME:** Matrix effect; **MQC:** Middle quantity control; **OATP2B1:** Organic anion transporting polypeptide; **P-gp:** Permeability-glycol protein; **PK:** Pharmacokinetics; **POD:** Peroxidase; **PPAR-?:** Peroxisome proliferator-activated receptor gamma; **P38-MAPK:** P38 mitogen-activated protein kinases; **QC:** Quantity control; **RP-UFLC:** Revers phase-ultra fast liquid chromatography; **RSD:** Relative standard deviation; **SD:** Standard deviation; **T1DM:** Type 1 diabetes mellitus; **T2DM:** Type 2 diabetes mellitus; **Tmax:** Time of maximum; **TG:** Triglycerides; **T-Chol:** Total cholesterol; **Vd:** Volume of distribution; **VLDL:** Very low lipid level.

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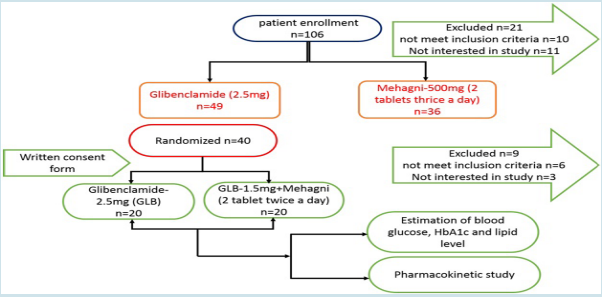
## PICTORIAL ABSTRACT




## SUMMARY

- Combination of allopathic and poly-herbal formulation has depicted a better control over diabetic complications with respect to allopathic formulation alone, and thus, this approach could be an alternative medication for T2DM.

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