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# POTENTIAL ROLE OF *MORUS INDICA* ADJUNCT THERAPY IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

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## ABSTRACT

*Morus indica* is used in Indian and Chinese medicine since centuries owing to its chemical and pharmacological properties. We hypothesize that *Morus indica* as an adjuvant with conventional anti-diabetic treatment will ameliorate favorably the hyperglycemia, oxidative stress and lipid abnormalities in type 2 diabetes mellitus. 30 type 2 diabetes mellitus subjects participated in a single-blind, placebo-controlled, randomized study to validate the observations of our previous studies. Subjects treated with oral hypoglycemic drugs (OHA) and insulin (INS) were supplemented with 6 gm of *Morus indica* for 8 weeks .Significant reduction in hyperglycemia was observed in *Morus* treated groups as compared to placebo. A marked fall in blood glucose was seen in subjects treated with insulin (48%) compared to OHA group (34.4%). The post-prandial blood glucose and HbA1c, after 8 weeks were significantly ($p<0.05$) low compared to the initial levels. In addition, **s**erum total cholesterol, triglycerides and lipid peroxides were significantly lowered in both the MIP treated groups as compared to placebo. *Morus indica* was well tolerated with creatinine, blood urea remaining unchanged in both groups. *Morus indica* effectively attenuated hyperglycemia and the dyslipidemia associated with diabetes without side effects and hence can be used as an adjuvant therapy in type 2 diabetes mellitus.

## KEYWORDS

*Morus indica*, medicinal plants, Type 2 diabetes and hyperglycemia.

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## INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder, with a significant impact on the health, quality of life and life expectancy of patients, as well as on the health care system. Insulin and various oral anti-diabetic agents such as sulphonylureas, metformin, α-glucosidase inhibitors, thiazolidinediones are the drugs commonly used in the management of diabetes[1,2].

Plants have been the basis of many traditional medicinal systems. Although more than 400 traditional plant treatments with anti-diabetic potential have been reported, only a small number of these have received scientific and medical evaluation to assess their efficacy[3,4]. Our research group has been screening several medicinal plants with a strong history of use in folklore medicine / traditional medicine for their anti- diabetic potential using *in vitro,* and *ex vivo* techniques before undertaking *in vivo* studies to confirm their role as alternative antidiabetic agents[5-12].

*Morus indica.*L (Mulberry), a fast growing deciduous plant has special importance in sericulture industry. It has been explored as a medicinal plant and its medicinal properties are testified in various scriptures. The leaves are nutritious, palatable, non toxic and also rich in various active principles[13]. Mulberry leaves and their components hold some interesting mechanism of action regarding their antidiabetic potential. *M. alba* is important with respect to antioxidant compounds[14-17]. Presence of phenolic compounds in general and flavonoids in particular, support the possible application of mulberry leaf extract and/ functional components to inhibit oxidation both *in vitro* and *in vivo*[18-21]. Mulberry teas are reported to inhibit α - glucosidase enzyme[22]. Prior to undertaking clinical trials, it is important that the blood glucose powering potential of a plant be evaluated in a systematic way using *in vitro, ex vivo* and *in vivo* models. Systematic studies to identify the mechanism of action of potential anti-diabetic plants are useful to validate and promote the use of such plants in the management of diabetes. Pre-clinical studies conducted in our laboratory have established the anti-diabetic potential and safety of *Morus indica* leaves[23,24].

The present study explores the anti-diabetic effect of *Morus indica* in type 2 diabetes mellitus subjects.

**Study Design**

A randomized, single-blind, free living study, with no changes with respect to medications or life style pattern was conducted. Patients with type 2 diabetes received 6g/day *Morus* tablets or placebo in addition to the conventional treatment with oral hypoglycemic (OHA) / insulin (INS) drugs for a period of 8 weeks. A total of 80 type 2 diabetic subjects attending the Primary Health Care centre of the University , were screened initially for diabetes, of which 30 were selected based on their fasting blood glucose (>7.77mmol/l), with the help of the attending physician. Subjects with a history of gastrointestinal problems, cardiovascular, renal or endocrine disorder (other than diabetes mellitus) were excluded from the study (Figure No.1).

Subjects were grouped as follows-

(i) Cont-OHA - Subjects on Oral hypoglycemic agents provided with placebo (n=8)

(ii) Expt-OHA – Subjects on Oral hypoglycemic provided with *Morus* (MIP) (n=10)

(iii) Cont-INS - Subjects on Insulin provided with placebo (n=6)

(iv) Exp-INS - Subjects on Insulin supplemented with the test material (n=6))

Subjects visited the health centre 5 times (one visit/15 days) during the study period. The subjects were advised to follow controlled dietary pattern. All subjects in OHA group were treated with the same class of hypoglycemic drug (sulfonylureas).

The protocol was approved by the University Human Ethics Committee (IHEC No 14/PhD/2007-08, 28 Feb 2008), informed consent was obtained from the subjects. At trial start and after 8 weeks, somatic measures, total body fat (TBF), visceral fat (VF) and basal metabolic rate (BMR), lipid profile, urea, creatinine, Hb A1c of the subjects were analyzed. Fasting blood glucose levels were monitored at the start of the trial and thereafter at 2 weeks intervals. Blood glucose was measured using the GOD/POD assay, HbA1c by HPLC, lipid peroxides[25] and glutathione[26] by colorimetric assay. Results were analyzed for significant differences by student's 't' test and one way ANOVA using SPSS software.

**RESULTS**

The baseline characteristics of all the participants in the study did not differ. The mean age of the subjects ranged from 49.6 - 51.5 y (Table No.1).

**Effect of *Morus* supplementation on glycemia**

The changes in fasting blood glucose levels during the study period are presented in table No.2.The fall in the mean fasting blood glucose was more marked in subjects supplemented with MIP. A significant ($p<0.05$) reduction in the blood glucose levels was observed in both Expt-OHA and Expt-INS groups. In the Expt-OHA group, there was a significant decrease at the end of 15 days of the study period, after which there was a gradual reduction, the fasting glucose decreased from an initial level of 7.49 ± 0.51 to 6.99 ± 1.88mmol/l. In Expt-INS group also, there was a significant ($p<0.05$) decrease at each interval of time, it was observed that the blood glucose decreased from an initial level of 10.19 ± 0.26 to 5.28±0.62mmol/l. While, in control groups there was no significant ($p<0.05$) decrease in the blood glucose levels. The percent reduction in the blood glucose levels in Expt-OHA and Expt-INS was 34.4 and 48% respectively. It was also observed that the post prandial blood sugar analyzed at the end of the study period was significantly ($p<0.05$) low compared to that of the initial levels in both the experimental groups (Figure No.2).

**Changes in Glycated haemoglobin (HbA1c)**

Consumption of *Morus indica* powder (MIP) significantly ($p<0.05$) reduced the $HbA_{1c}$ compared with placebo (Figure No.3). The mean values reduced from an initial level of 8.55 ± to 6.18% and 8.62 to 6.64% in Expt-OHA and Expt-INS groups, respectively. However, there was no significant reduction in the HbA1c in the control subjects. Despite the short duration of treatment (8 wk) a significant reduction in $HbA_{1c}$ levels was observed.

**Lipid profile and biochemical parameters**

The mean serum total cholesterol, triglycerides, urea and creatinine levels at the start and end of the study are given in Table No.3.

MIP supplementation significantly ($p<0.05$) reduced serum total cholesterol and triglycerides in the experimental groups, while there were no changes in the control groups. Total cholesterol reduced by 15 and 20% and triglycerides reduced by 40 and 34% in Expt-OHA and Expt-INS groups, respectively. Though there was decrease in urea and creatinine values, it was not significant, except for creatinine in Expt-INS group which showed significant decrease.

**Oxidative stress and glutathione**

MIP therapy could inhibit malonaldehyde (MDA) formation and also could increase the glutathione (GSH) levels significantly ($p<0.05$) in the experimental groups (Table No.4). The formation of MDA in both experimental groups (4.34 ± 0.16 and 5.26 ± 0.23nm/ml) was significantly low compared to the control groups (5.08 ± 0.26 and 6.23 ± 0.16nm/ml). The GSH levels in the serum of the Expt-OHA was significantly ($p<0.05$) high (0.38 ± 0.06mM/ml) compared to Cont-OHA (0.26 ± 0.10mM/ml), whereas, significant difference was not observed in the INS groups.

## DISCUSSION

The present single blind study in type 2 diabetic subjects validates the observed anti-diabetic properties of *Morus indica* as indicated by *in vitro, ex vivo* and animal studies[23,24]. The dosage of the sample was finalized based on the *in vivo* animal study[24]. The subjects were counseled to consume the sample (tablet form) and placebo before breakfast and dinner daily for 8 weeks. There were no adverse effects or complaints made by the patients during the study. Post supplementation, subjects reported that common complaints such as generalized weakness, gastric discomfort and constipation had gradually subsided. In addition, MIP therapy indicated many beneficial effects on the glycemic and lipidemic status of the patient.

Diabetes Mellitus, is a heterogenous disorder associated with glucose intolerance, hyperglycemia, acute metabolic and chronic complications affecting many organs of the body[27]. MIP therapy showed a gradual and significant reduction in the blood glucose levels in the experimental groups. The subjects of all the experimental groups were on their conventional hypoglycemic drugs. Therefore, this indicates the added advantage of the MIP therapy on patient's glycemic status. Also, a significant decrease in the post - prandial blood

glucose at the end of the study period was seen compared to the base line levels in the experimental subjects, suggesting that MIP could overcome postprandial hyperglycemia which is one of the major cause for the initiation and progression of diabetic complications[28].

As dyslipidemia plays a role in the long term complications of diabetes, its correction is considered beneficial. Studies report that diabetic state, resulting from impaired secretion and sensitivity of insulin may be responsible for high triglycerides level in serum, as the insulin stimulate the synthesis of adipose tissue through lipoprotein lipase[29]. Saponins may compete with cholesterol at the binding site or interfere with cholesterol biosynthesis in liver and thus exert the hypocholesterolemic effect. Soluble fibers like gums, pectins, mucilages may block cholesterol absorption in the intestine[30]. A study reports that presence of dietary fiber in fenugreek seeds (*Trigonella foenum graecum*), bitter gourd (*Momordica charanti*) and jambu seeds *(Syzygium cumini*) may affect the serum cholesterol by reducing cholesterol and bile acid absorption, by altering the metabolism and ratio of bile acid absorbed and by altering the intestinal secretion and hepatic production of lipoprotein[31]. Studies report the lipid lowering effect of fenugreek seeds in hyperlipidemic type 2 diabetic subjects[32], attributing the hypolipidemic effect to the inhibition of the lipogenic and cholesterogenic enzymes and the increased fecal excretion of cholesterol[28]. Statins, frequently used to lower blood cholesterol levels are highly effective, however, are reported to cause side effects such as muscle pain, digestive problems and mental fuzziness in some people and may rarely cause liver damage[33]. MIP supplementation for 8 weeks reduced the total cholesterol and triglyceride levels, significantly. Though the exact mechanism is not clear, the hypolipidemic effect of the sample may be due to the presence of phytochemicals.

It is reported that one of the active component present in *Morus indica* is 'fagomine', which might be responsible for its hypoglycemic effect[34]. It is reported that blood cholesterol levels are influenced by the both the quality and quantity of protein in the diets, plant protein are effective in lowering cholesterol level[35]. Further, a high proportion of diabetic patients in tropics and subtropics suffer from malnutrition. Since *Morus* was found to be a good source of antioxidant components, protein (24%) and also fiber (16%), supplementation of the whole leaf powder instead of providing only the isolated components will have the added nutrient advantage. Reductions in blood glucose achieved with a relatively low pharmacological concentration of MIP, indicates that *Morus indica* offers multiple therapeutic benefits, hence can be used as an adjunct or as a functional food in the management of diabetes mellitus. Herbal drugs are cheap, easily available without any adverse or toxic effect. Though, it was not within the scope of the study to identify the bioactive compound responsible for the observed therapeutic benefit, clinical studies attribute the therapeutic properties to the presence of flavonoids, alkaloids and steroids in mulberry[36]. Our findings are in agreement of the results of an earlier study[37], which reports significant improvement in glycemic control and more pronounced effect on lipid profile on supplementation of mulberry leaves for 30 days. In this study, *Morus indica* was given as an adjuvant with antidiabetic medication for a longer time (8 weeks), due to which significant improvement in lipid profile and $HbA_{1c}$ were observed.

Based on our *in vitro* and *in vivo* studies, it is suggested that the viscous fiber and polyphenols of *Morus indica* exert anti-diabetic effect by delaying post-prandial glucose absorption, inhibiting enteric enzymes and promoting insulin secretagouge effect.

**Table No.1: Somatic, clinical and biochemical characteristics of the subjects**

| S.No | | Subjects on OHA | | Insulin treated subjects | |
|---|---|---|---|---|---|
| | | Control | Experimental | Control | Experimental |
| 1 | No. of subjects | 8 | 10 | 6 | 6 |
| 2 | Male: Female | 6:2 | 5:5 | 3:3 | 4:2 |
| 3 | Mean age (y) | 50.25± 6.4 | 49.6±3.3 | 51.5± 7.3 | 51.4± 4.6 |
| 4 | Duration of Diabetes (y) | 6.2± 2.32 | 5.8± 1.46 | 7.2± 1.5 | 7.6± 1.4 |
| 5 | Body Mass Index(BMI) | 28.0± 4.81 | 24.5± 3.60 | 29.4± 3.80 | 27.7± 3.70 |
| 6 | Fasting Blood Glucose (mmol/l) | 6.44± 1.69 | 7.16± 0.57 | 9.02±0.45 | 7.84± 0.25 |
| 7 | Systolic Blood Pressure (mm Hg) | 148±16.11 | 152±14.10 | 158±20.10 | 152±15.11 |
| 8 | Diastolic Blood Pressure (mm Hg) | 96±8.44 | 98± 6.34 | 104±2.64 | 102±2.34 |
| 9 | Mean HbA1c (%) | 7± 0.87 | 8.55± 1.14 | 8.30± 1.78 | 8.62± 0.92 |

**Table No.2: Impact of *Morus indica* supplementation on fasting blood glucose in type 2 diabetic subjects**

| S.No | Group | Fasting blood glucose (mmol/l) | | | | |
|---|---|---|---|---|---|---|
| | | Initial | 2nd Week | 4th Week | 6th Week | 8th Week |
| 1 | Cont - OHA | $6.45^{a}$ ± 1.69 | $6.24^{a}$ ± 0.95 | $6.86^{a}$ ± 1.65 | $7.03^{a}$ ± 2.31 | $6.99^{a}$ ± 1.88 |
| 2 | Expt- OHA | $7.49^{a}$ ±0.57 | $4.97^{b}$ ±0.94 | $5.03^{b}$ ±0.49 | $5.07^{b}$ ±0.58 | $4.91^{b}$ ±0.60 |
| 3 | Cont - INS | $9.01^{a}$ ±3.45 | $9.25^{a}$ ±2.71 | $9.56^{a}$ ±2.94 | $9.45^{a}$ ±3.45 | $9.88^{a}$ ±3.88 |
| 4 | Expt- Expt | $7.84^{a}$ ±0.25 | $8.94^{b}$ ±0.65 | $6.42^{c}$ ±0.43 | $5.17^{d}$ ±0.42 | $5.28^{d}$ ±0.62 |

Mean values carrying superscripts a, b, c… in rows differ significantly (P<0.05).

Cont-OHA – control subjects on oral hypoglycemic agents

Expt-OHA – experimental subjects on oral hypoglycemic agents

Cont-INS – control subjects on insulin,

Expt-INS – experimental subjects on insulin

**Table No.3: Effect of *Morus indica* supplementation on the blood lipid profile, urea and creatinine in the subjects**

| S.No | Group | Total cholesterol (mg/dl) | | Triglycerids (mg/dl) | | Urea (mg/dl) | | Creatinine (mg/dl) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | Before | After | Before | After |
| 1 | Cont-OHA | $178.38^{a}$ ± 22.06 | $191.13^{a}$ ± 24.51 | $151.10^{a}$ ± 35.54 | $161.50^{a}$ ±38064 | $15.88^{a}$ ± 7.79 | $17.23^{a}$ ±8.62 | $0.76^{a}$ ± 0.20 | $0.86^{a}$ ± 0.17 |
| 2 | Expt-OHA | $188.9^{a}$ ±15.05 | $161.5^{b}$ ±19.74 | $175.0^{a}$ ±14.65 | $104.7^{b}$ ±31.92 | $24.2^{a}$ ±12.26 | $20.7^{a}$ ±7.72 | $1.07^{a}$ ±0.27 | $0.88^{a}$ ±0.23 |
| 3 | Cont-INS | $164.75^{a}$ ±39.15 | $189.25^{a}$ ±36.40 | $149.75^{a}$ ±33.71 | $178^{a}$ ±17.66 | $29.0^{a}$ ±5.35 | $30.62^{a}$ ±3.10 | $0.97^{a}$ ±0.04 | $1.12^{a}$ ±0.14 |
| 4 | Expt-INS | $198.8^{a}$ ±9.63 | $159.0^{b}$ ±14.92 | $204.8^{a}$ ±15.58 | $136.4^{b}$ ±34.44 | $32.6^{a}$ ±5.18 | $27.02^{a}$ ±5.02 | $1.26^{a}$ ±0.7 | $0.99^{b}$ ±0.14 |

**Table No.4: Serum lipid peroxides and Glutathione content in the subjects- Post supplementation**

| S.No | Groups | MDA (nM/ml) | GSH (mM/ml) |
|---|---|---|---|
| 1 | Cont-OHA | 5.08±0.26 | 0.26±0.10 |
| 2 | Expt-OHA | 4.34±0.16 | 0.38±0.06 |
| 3 | Cont-INS | 6.23±0.16 | 0.22±0.07 |
| 4 | Expt-INS | 5.26±0.23 | 0.26±0.08 |

MDA- Malondialdehyde, GSH- Glutathione

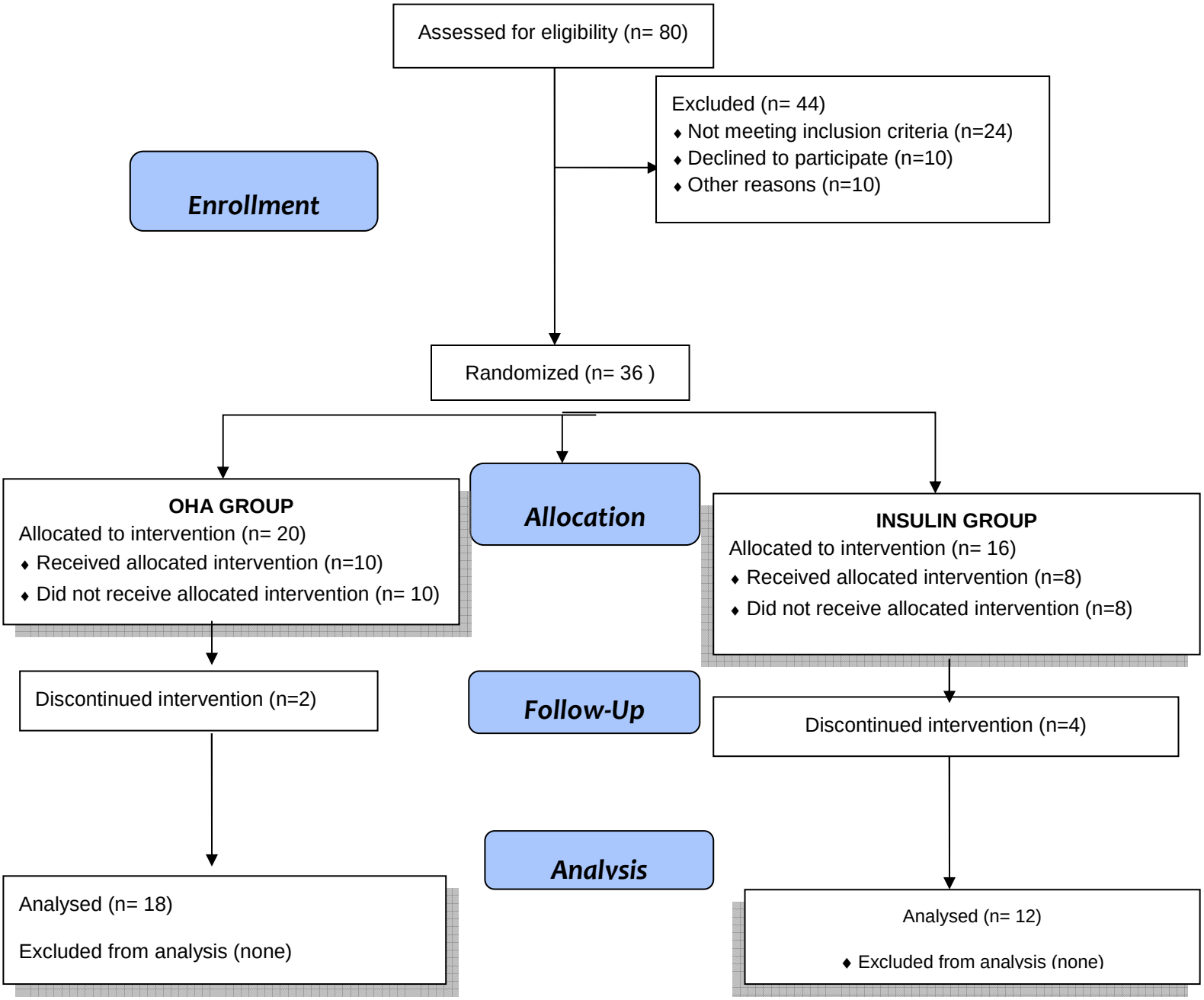


**Figure No.1: Study design**

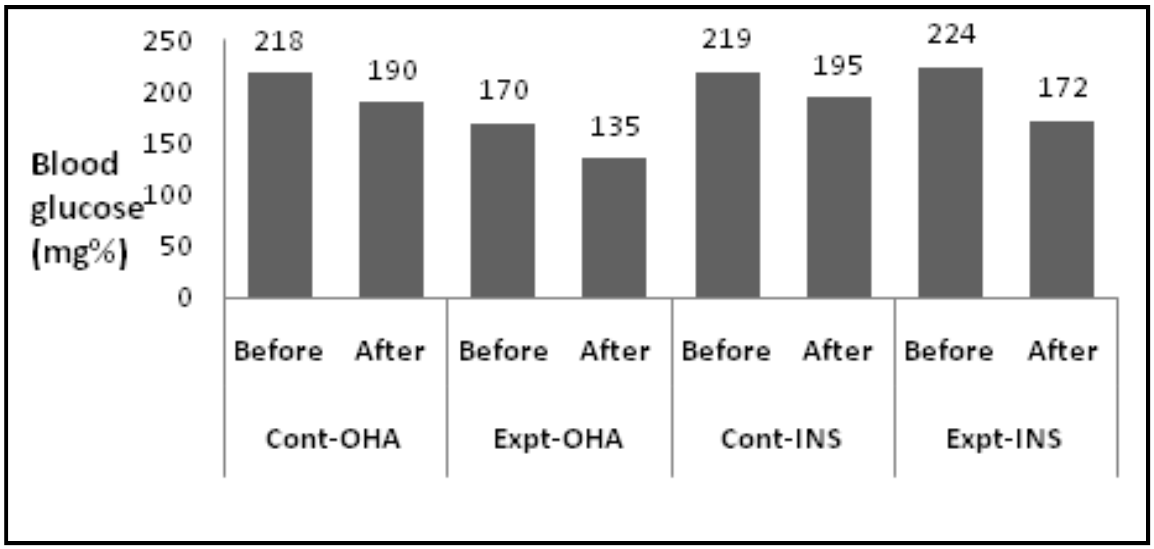


**Figure No.2: Effect of *Morus indica* supplementation on post prandial blood glucose in type 2 diabetic subjects**

Cont-OHA – control subjects on oral hypoglycemic agents
Expt-OHA – experimental subjects on oral hypoglycemic agents
Cont-INS – control subjects on insulin
Expt-INS – experimental subjects on insulin

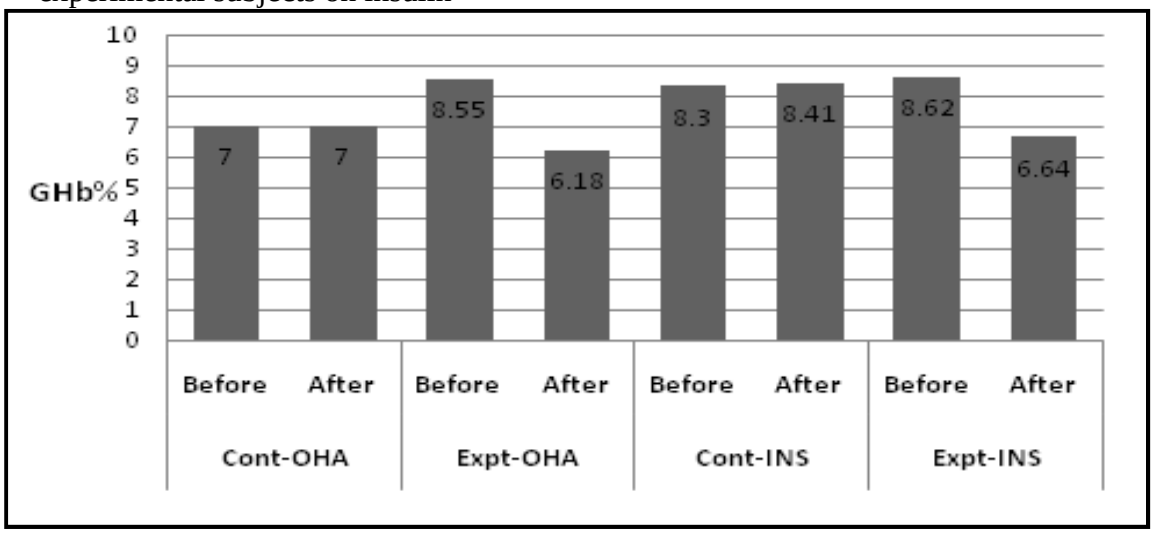


**Figure No.3: Changes in Glycated haemoglobinin the subjects**

## CONCLUSION

The research on medicinal plants *per se* could provide useful leads towards the development of newer alternatives for the treatment of diabetes. From the present study, it may be concluded that *Morus Indica* has many beneficial properties hence, has scope to be developed as a viable alternate therapy for diabetes.

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## CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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