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Ficus Racemosa and *Morus indica*: Emerging Alternative Antihyperglycemic Agents

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Abstract: Despite the great strides made in the understanding and management of diabetes, the disease and disease-related complications are increasing unabated. Phytochemicals identified from traditional medicinal plants are presenting an exciting opportunity for the development of new types of therapeutics. Our research group has explored the possible mechanisms of antidiabetic action of two medicinal plants viz., *Ficus racemosa* bark (FRB) and *Morus indica* leaves (MI), known to possess antihyperglycemic effect using simple in vitro techniques followed by pre-clinical and clinical studies. Both plants exhibited good glucose adsorption capacity, retarded glucose diffusion, inhibited enteric enzymes viz., α-amylase, α-glucosidase and sucrase emphasizing that inhibition of carbohydrate hydrolyzing enzymes is one of the mechanisms of hypoglycemic action of FRB and MI. Further, both FRB and MI demonstrated significant antihyperglycemic activity in streptozotocin-induced diabetic rats associated with significant elevation in serum insulin. The samples also exhibited cholesterol and triglyceride lowering effect. In clinical trials, the antihyperglycemic effect was consistent which resulted in good glycemic control compared to control group.These observations prompted us to postulate the possible mechanism of antihyperglycemic action of the plants to be inhibition of digestion and absorption of dietary carbohydrates in the intestine, modulation of carbohydrate metabolizing enzymes, augmenting insulin synthesis and increasing peripheral utilization of glucose. These studies have provided adequate scientific evidence supporting the usage of these medicinal plants for the treatment of Type 2 Diabetes Mellitus in traditional system of medicines.

Keywords: Diabetes, *Ficus racemosa*, hyperglycemia, *Morus indica*, phytochemicals.

INTRODUCTION

Diabetes mellitus is a chronic disease of absolute or relative insulin deficiency or resistance characterized by disturbances in carbohydrate, protein and fat metabolism. Research in the field is wide-spread ranging from causes to treatment. The prevalence of diabetes is rising exponentially. Despite achievements in treatment modalities the search for new and effective therapies with less side effects still continues.

Research will help improve the delivery of diabetes care and address the gap between developmental and clinical trial research and "real-world" implementation. Diabetes translational research is an exciting area, the outcomes of which can prevent much morbidity and suffering. Translation occurs in two continuous phases. The first is “bench to bedside,” i.e., from laboratory research to clinical research application, the second is from the ‘clinical research setting to real-world practice’. Given the alarming increase in the rate of diabetes both nationally and internationally, this is a timely and important mission [1]. Ongoing research across the world is uncovering new insights into diabetes and opening the door for prevention and better therapies. Progress in understanding the metabolic staging of diabetes over the past few years has led to significant advances in treatment regimen. In Vitro Disease Pharmacology CROs offer effective systems to screen pre-clinical candidates without the costs and time associated with *in vivo* models.

Phytochemicals identified from traditional medicinal plants are presenting an exciting opportunity for the development of newer therapeutics. Isolated islets have formed an effective in vitro model in antidiabetic drug development program, screening of potential hypoglycemic agents and for investigating their mechanisms of action. In recent years, molecular biological techniques have produced a large number of new animal models for the study of diabetes, including knock-in, generalized knock-out and tissue-specific knockout mice. The field of regenerative medicine is rapidly advancing by the potential to reprogram one cell type into another, with implications for diabetes.

The promise of prevention, treatment, and cure for diabetes can only be realized through the vigorous support of scientific research [2]. In view of this, a comprehensive account of conventional therapies and alternative approaches for the treatment of diabetes is presented and the potential of *Ficus racemosa* bark and *Morus indica* leaves to be used as adjuncts in the management of Type 2 Diabetes Mellitus (T2DM) are discussed.

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Conventional therapies: Lifestyle management is at the forefront of therapy options. In addition to exercise, weight control, medical nutrition therapy, oral glucose-lowering drugs and insulin are the conventional therapies. Since the most important pathological process during the development of diabetes involves three key organs, i.e., pancreatic islets, liver and skeletal muscle, almost all anti-diabetic therapies are aimed at these organs. T2DM often co-exists with hypertension and dyslipidemia increasing the risk for cardiovascular complications. Modulation of these risk variables may prove beneficial in reducing the CVD risk in T2DM [3, 4]. Alternative approaches with anti-diabetic activity have been researched extensively, particularly in India. Ideal therapies should have a similar degree of efficacy without the troublesome side effects associated with conventional treatments. Alternative therapies for diabetes have become increasingly popular in the last several years, including medicinal herbs, nutritional supplementation, acupunture and hot tub therapy [5, 6].

Controversies: It is common practice for clinicians to prescribe drugs such oral hypoglycemic agents and or insulin to achieve glycemic control. Many patients are using alternative therapies including dietary supplements or complementary and alternative medicine treatment. However, the safety and efficacy of alternative therapies in general and of medicinal plants in particular must be evaluated by rigorous clinical investigations to confirm and advocate the excellence over the conventional therapies. Medicinal herbs with antihyperglycemic activities are increasingly sought by diabetic subjects and health care professionals and the market for herbal medicines is expanding globally, it is being simultaneously counterbalanced by inadequate regulation [7].

Research objectives: Our research group has been screening several medicinal plants with a strong history of use in folklore medicine / traditional medicine and studied their potential using simple *in vitro* and *ex vivo* techniques before undertaking *in vivo* studies to confirm their role as alternative antidiabetic agents. Various dietary fiber sources and medicinal plants such as *Plantago ovata*, *oats*, *barley*, *Gymnema sylvestrae*, *Tinospora cardifolia*, *Eugenia jambulana*, *Ficus racemosa*, *Aegle marmelos*, *Butea monosperma*, *Ficus benghalensis* and *Moringa oleifera* have shown promising antidiabetic effect *in vitro* [8-16]. Ficus racemosa bark (FRB) and *Morus indica* leaf (MI) were further studied for their efficacy and safety as possible adjuncts and/or alternatives for T2DM.

Ficus racemosa Linn. (Moraceae) is an evergreen, moderate to large sized spreading, lactiferous, deciduous tree commonly known as 'Gular' [17]. All parts of this plant are regarded medicinally important in Ayurveda and has been used extensively in the treatment of biliary disorders, jaundice, dysentery, diabetes, diarrhea and inflammatory conditions [18-20]. Antidiabetic potential of various parts of *F. racemosa* has been studied in diabetic rats/rabbits. The antidiabetic potential of the stem bark is reported by several workers. Aqueous and ethanol extracts of the stem bark have exhibited long term antihyperglycemic effect in alloxan-induced diabetic rats [21]. Similarly, methanol extracts of the stem bark has shown significant hypoglycemic effect in both normal and alloxan-induced diabetic rats, comparable to that of glibenclamide, a standard antidiabetic drug [22]. In addition to reducing blood glucose, ethanol extracts were effective in lowering serum lipids and lipoproteins to near normal levels [23]. Feeding of ethanol root extract caused a significant decrease in blood glucose in alloxan induced diabetic rats [24]. A study on diabetic rabbits reports significant hypoglycemic effect of a compound recipe of medicinal plants containing *F. racemosa* [25].

Morus indica (MI), commonly known as mulberry plant (Morus spp. L., Moraceae) has been domesticated over thousands of years and adapted to the wide area of tropical, subtropical, and temperate zones of Asia, Europe, North and South America, and Africa. The fruits, roots and bark of mulberry have been used in folk medicine to treat diabetes, hypotension, anemia and arthritis [26].

Morus species (mulberry), occupies an important position in Indian and Oriental medicine. Mulberry leaves and their components hold some interesting mechanism of action regarding their antidiabetic potential. The extracts of *Morus indica* L, and Moran 20k a purified protein from *Morus alba* root extract possess hypoglycemic, hypotensive, antioxidant and diuretic activities [27]. Mulberry feeding in type 2 diabetics improved blood glucose and lipid profile [28]. In recent years, tea from the mulberry leaves is gaining attention in Asian countries as an antidiabetic drink, it is reported to inhibit various enzymes such as α – glucosidase, sucrase and maltase [29].

These two plants were selected for further investigation based upon the available data and our experience of studying the *in vitro* starch digestibility and factors affecting it including dietary fiber content and *in vivo* glycemic responses of Indian foods and more recent work on the *in vitro* hypoglycemic effects of plants used in traditional medicine in India. It was also noted that, although *F. racemosa* bark and *M. indica* leaves are being used for the treatment of diabetes since prehistoric times, limited scientific data was available on its efficacy. Thus, they were systematically evaluated for their antidiabetic potential using *in vitro, ex vivo,* and *in vivo* model systems to ascertain the mechanism of its antihyperglycemic action. Furthermore, a double blinded placebo controlled clinical trial was also undertaken to evaluate its clinical efficacy.

METHODOLOGY

Preclinical Studies

1. *In vitro* and *ex vivo* assays: The samples were screened for their hypoglycemic potential using several assays such as : glucose adsorption capacity, retardation of glucose diffusion, enteric enzyme inhibition (α-amylase, glucosidase and sucrase) glucose uptake and transport. The methods are described in our earlier publications [14, 15].

2. Animal studies: The antidiabetic, antioxidant and lipid lowering effects of *Ficus racemosa* (FRB)and *Morus indica* (MI) was studied in streptozotocin (STZ) induced type-2 diabetic rats and compared with that of conventional hypoglycemic agents (Insulin and Glibenclamide). Experimental diabetes was induced by a single intraperitonial injection of streptozotocin (55 mg/kg). The experimental design is explained in earlier publications [30-33]. The STZ diabetic rats were administered orally with F. *racemosa* bark

Fig. (1). Effect of *Ficus racemosa* and *Morus indica* on blood glucose in streptozotocin-induced diabetic rats. FRB: Ficus racemosa bark, MI: Morus indica leaf, DC: diabetic control, INS: insulin, GBN: glibenclamide.

powder, aqueous extract, *M indica* leaf powder. Glucose, glutathione, lipid profile, glucose-6-phospahte dehydrogenase, aldolase and thiobarbituric acid reactive substances (TBARS) in serum and liver were estimated following the established procedures. Biochemical observations were supplemented with histological examination of pancreatic tissue. All animal procedures have been approved by the Animal Ethics committee of the University of Mysore.

Clinical studies: The studies used a free-living, single / double blinded, randomized placebo controlled designs approved by the Institutional Human Ethics Committee of the University of Mysore (IHEC No's 14 and 15- PhD/2007-08, 28.2.2008). Subjects with documented type 2 diabetes managed on oral hypoglycemic drugs, without any complications of diabetes were recruited from a diabetic clinic and University Health centre in Mysore city, India. Eligible participants were enrolled in the study and provided informed consent. The detailed study design is described elsewhere [34, 35]. The subjects consumed 1 capsule of *F racemosa* (400 mg) thrice daily or *M Indica* leaf powder (6g) before each meal for a period of 8 weeks. They were observed for any adverse effects and clinical symptoms by weekly follow-up visits. Biochemical parameters viz., fasting and post-prandial glucose, lipid profile, serum insulin, lipid peroxides and glutathione were assessed before and after the supplementation.

RESULTS

Pre-Clinical Studies

In vitro hypoglycemic studies indicated higher glucose adsorption capacity resulting in higher retardation of glucose diffusion. The liberation of glucose was greatly inhibited by FRB in amylolysis kinetics. Furthermore, it increased the rate of glucose transport across the yeast cell membrane and in isolated rat hemi-diaphragm and inhibited α-amylase, α-glucosidase, β-glucosidase and sucrase in a dose dependent manner indicating a strong hypoglycemic effect *in vitro* and *ex vivo* [13-15]. Similar observations were noted with reference to *Morus indica*, wherein the sample effectively inhibited the digestion of starch and also inhibited the movement of liberated glucose across the dialysis membrane which could be attributed to the inhibition of carbohydrate hydrolyzing enzymes. Further, *Morus indica* also enhanced the glucose uptake in yeast cells indicating the enhancement of peripheral utilization of glucose by the target cells [35].

The beneficial effects of dietary fibers in modulating glycemic responses is attributed to their water holding capacity and high viscosity in the gastrointestinal tract. These properties are dependent on fiber concentration, molecular weight and also size- distribution of fiber-gum particles [36].

The antidiabetic effect of functional ingredients might be due to adsorption of glucose, retardation of glucose diffusion, inhibition of carbohydrate hydrolyzing enzymes, modulation of carbohydrate metabolizing enzymes, augmenting insulin secretion and increasing the glucose uptake in the target cells [8-16].

CLINICAL STUDIES

Animal studies: The long term antihyperglycemic, lipid lowering and antioxidant effect of FRB and MI was studied in streptozotocin-induced diabetic rats. Oral administration of FRB and MI (500 mg kg-1 BW) for 6 weeks decreased fasting blood glucose by >50%. The aqueous extract was more effective and caused a significant reduction in TBARS, AST, ALT levels compared to untreated diabetic rats. An increase in glutathione concentrations over the control levels was also observed in rats treated with FRB and MI (Fig. **1**). Serum insulin levels were increased to near normal levels (Fig. **2**). These observations were supported by the

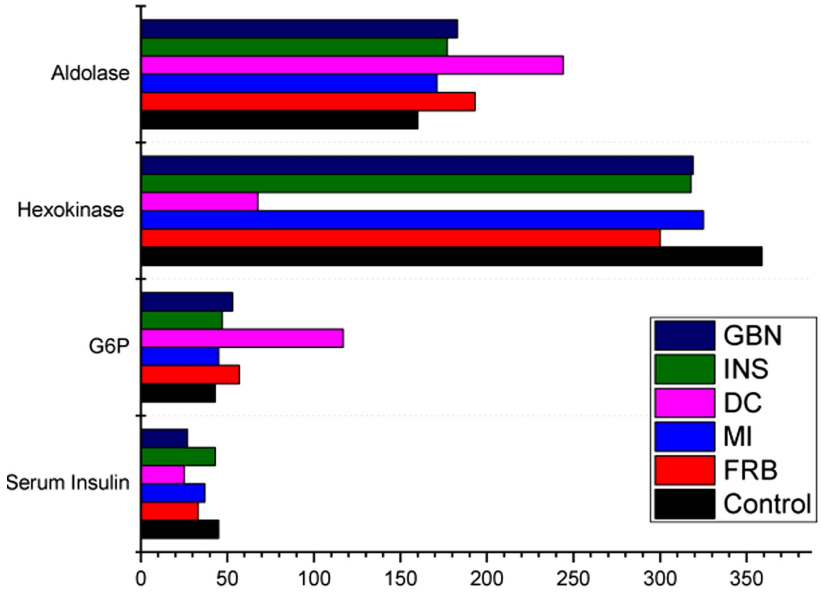

Fig. (2). Effect of on *Ficus racemosa* and *Morus indica* on serum insulin and enzymes of carbohydrate metabolism. Control: non diabetic rats, FRB: Ficus racemosa bark MI: Morus indica,, DC: untreated diabetic rats, INS: insulin treated diabetic rats, GBN: glibenclamide treated diabetic rats. G6P: Nmoles of Pi liberated /min/mg protein, Hexokinase: Nmoles of glucose-6-phosphate formed/min/mg protein, Aldolase: Nmoles of glyceraldehydes formed /min/mg protein.

Table 1. Impact of Medicinal Plants on Biochemical Parameters in STZ Rats

Rat Group	Total Protein (g/dl)	Albumin (g/dl)	Urea mg/dl	Creatinine mg/dl	Total Cholesterol mg/dl	TG mg/dl	TBARS nm/mg	GSH µm/mg P
Control	6.8 ^{c} ±1.00	3.6 ^{a} ±0.40	23.03 ^{a} ±1.47	0.80 ^{a} ±0.07	57.3 ^{bc} ±4.23	104 ^{a} ±9.40	0.08 ^{a} ±0.01	0.27 ^{cd} ±0.26
DC	4.48 ^{a} ±0.51	5.4 ^{b} ±0.62	68.90 ^{d} ±4.00	1.16 ^{b} ±0.20	100.4 ^{d} ±5.30	143 ^{c} ±11.9	0.29 ^{c} ±0.03	0.05 ^{a} ±0.01
FRP	6.1 ^{bc} ±1.00	3.5 ^{a} ±0.31	59.30 ^{c} ±4.70	0.86 ^{a} ±0.4	57.1 ^{bc} ±4.70	103 ^{a} ±4.80	0.10 ^{a} ±0.03	0.20 ^{c} ±0.01
FRAE	6.4 ^{c} ±0.43	3.8 ^{a} ±0.30	40.60 ^{b} ±5.7	0.82 ^{a} ±0.2	55.5 ^{b} ±4.36	99 ^{a} ±10.8	0.15 ^{b} ±0.01	0.22 ^{c} ±0.01
MIP	6.7 ^{c} ±0.72	3.8 ^{a} ±0.24	42.80 ^{b} ±11.9	0.78 ^{a} ±0.30	47.0 ^{a} ±3.90	107.3 ^{a} ±6.6	0.10 ^{a} ±0.03	0.18 ^{b} ±0.05
INS	6.09 ^{bc} ±0.33	3.72 ^{a} ±0.12	35.45 ^{b} ±5.3	0.80 ^{a} ±0.10	60.2 ^{c} ±5.28	117 ^{b} ±11.2	0.15 ^{b} ±0.02	0.17 ^{b} ±0.03
GBN	5.8 ^{b} ±0.31	3.32 ^{a} ±0.64	36.20 ^{b} ±7.2	1.24 ^{b} ±0.30	56.0 ^{bc} ±3.34	80.2 ^{a} ±16.8	0.21 ^{c} ±0.06	0.17 ^{b} ±0.03

TG-Triglycerides, TBARS- thiobarbituric reactive substances, GSH- glutathione
DC- Diabetic control, FRP- *Ficus racemosa* powder, FRAE- *Ficus racemosa* aqueous extract, MIP-*Morus indica* powder INS- insulin , GBN- glibenclamide
Values are Mean ± SD (n=6), values carrying superscripts a, b, c and d in columns differ significantly ($p<0.05$).

histopathological profiles of the pancreas wherein, both FRB and MI significantly ($p<0.05$) reduced inflammatory and degenerative changes compared to untreated diabetic rats.

Both FRB and MI restored the activities of glucose-6-phosphatase, aldolase, glucose-6-phosphate dehydrogenase and hexokinase compared to untreated diabetic rats (Fig. **2**). The concurrent effect of FRB and MI on lipid metabolism was significant in diabetic animals, this was evidenced by the reduction of serum cholesterol, triglycerides and lipid peroxides in animals treated with medicinal plants (Table **1**). In the present study, TBARS levels were significantly increased and antioxidants were decreased in diabetic rats. Treatment with *F racemosa* and *Morus indica* effectively reduced serum AsAT and AlAT activities suggesting that the plant could prevent hepatic injury associated with diabetes [24-26]. The decreased serum protein, albumin and the increased urea, creatinine levels in STZ rats were restored to normal levels (Table **1**).

Table 2. Changes in Blood Glucose Levels in Type 2 Diabetic Subjects Treated with *Morus*

Group	Fasting Blood Glucose (mg/dl)				
	Initial	**2nd Week**	**4th Week**	**6th Week**	**8th Week**
Cont -OHA	116.13[a] ± 30.61	112.5[a] ± 17.21	123.63[a] ± 29.7	126.75[a] ± 41.66	126.0[a] ±33.97
Expt -OHA	135[a] ± 9.33	89.5[b] ± 16.99	90.7[b] ±8.97	91.5[b] ± 10.50	88.5[b] ±10.90
Cont -INS	162.5[a] ± 62.21	166.75[a] ± 48.92	172.30[a] ± 53.09	170.25[a] ± 62.28	178.14[a] ± 70.06
Expt -INS	183.6[a] ± 4.62	161.21[b] ± 11.79	115.8[c] ± 7.91	93.18[d] ± 7.65	95.2[d] ±11.23

Mean values carrying superscripts a, b, c… in rows differ significantly.
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

Human studies: Based on the results of the *in vitro, ex vivo* and animal studies, single/double blinded placebo controlled human studies were undertaken to validate the antihyperglycemic efficacy of *F. racemosa* aqueous extract and *M. indica* leaf powder in Type 2 Diabetic subjects.

The subjects managed on oral hypoglycemic drugs without any documented complications were recruited from a diabetic clinic and University health centre in Mysore city. The subjects consumed 1 capsule (400 mg) thrice daily and MI leaf powder (6g) before each meal for a period of 8 weeks. They were observed for any adverse effects and clinical symptoms by weekly follow-up visits.

No modifications were made in their regular food and exercise pattern. The study clearly demonstrated the antihyperglycemic effect of aqueous extract of *F. racemosa* bark and MI leaf powder in humans as evidenced by improved glycemic control. It was observed that a significant reduction in fasting and postprandial blood glucose was achieved by their consumption. Furthermore, a significant increase in serum insulin level was observed in the experimental groups compared to control groups. These findings are suggestive of the facts that, both *F. racemosa* bark and *Morus indica* leaf possesses good antihyper-glycemic effect in type II diabetic subjects by augmenting serum insulin. The beneficial effect of Morus may be due to several factors, as follows, Morus contains highly viscous fiber that delays post-prandial glucose absorption, polyphenol present in the plant inhibit carbohydrate hydrolyzing enzymes and might exert insulin secretagouge effect [27, 28]. MI therapy showed a gradual and significant reduction in the blood glucose levels of the experimental subjects (Table **2**).

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 initial levels in the experimental subjects. This suggests that MI could overcome postprandial hyperglycemia which is one of the major causes for the initiation and progression of many diabetic complications. The hypoglycemic effect of MIP was studied using some *in vitro* techniques, wherein, the glucose adsorption capacity of the sample was tested at different concentration (5, 10, 20 and 50mM) of glucose which simulates the various levels of hyperglycemia. It was observed that as the concentration of the glucose increased the glucose adsorption capacity also increased, indicating that antihyperglycemic effect of MI [35]. The above effect of *Ficus racemosa* and *Morus indica* may be due to insulin release from pancreatic β–cells, inhibition of glucose absorption in gut, stimulation of glycogenesis in the liver or increased utilization of glucose by the body. These medicinal plants are also reported to exhibit their antioxidant, hypolipidemic, restored enzymatic functions, repair and regeneration of pancreatic islets and the alleviation of liver and renal damage. Research on medicinal plants per se could provide useful leads towards the development of newer alternatives for the treatment.

From the present experimental data, it is evident that both *Ficus racemosa* bark and *Morus indica* leaves efficiently regulate blood glucose in diabetic rats by modulating the activity of carbohydrate metabolizing enzymes and also ameliorating lipid abnormalities associated with diabetes.

Proposed mechanisms: Based on the preclinical and clinical findings, it was proposed that the samples exert their antidiabetic effect by the following mechanisms (Fig. **3**).

- Increasing the viscosity of the intestinal contents causing adsorption of glucose molecules resulting in their entrapment and thereby reducing diffusion of glucose from the intestinal lumen into the blood the stream, consequently blunting postprandial hyperglycemia.
- Inhibiting carbohydrate hydrolyzing enzymes (α-amylase, α-glucosidase, β-glucosidase and sucrase) thereby limiting the digestion, delaying the release and absorption of glucose into the blood stream.

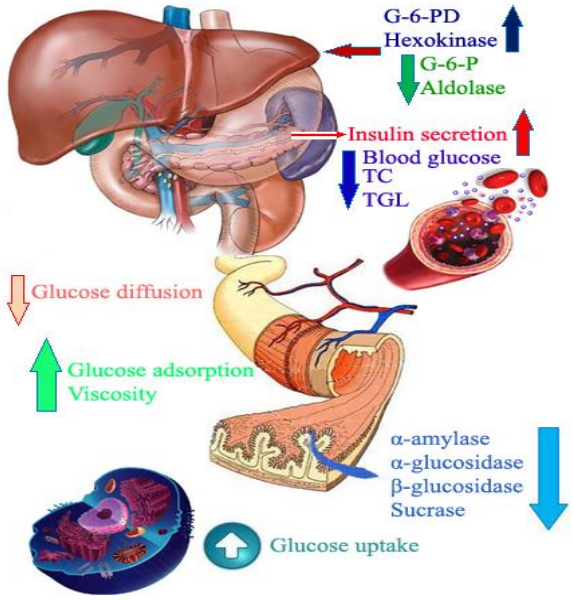

Fig. (3). Proposed mechanism of antihyperglycemic action of *Ficus racemosa* bark and *Morus indica* leaf. G-6-PD: glucose-6-phosphate dehydrogenase, G-6-P: glucose-6-phosphatase, TC: total cholesterol, TGL: triglycerides.

- Modulating the activity of carbohydrate metabolizing enzymes (glycolytic and gluconeogenic enzymes) consequently resulting in better utilization of glucose causing blunting of plasma glucose rise.
- Increases glucose uptake/transport across target cells resulting in increased peripheral utilization of glucose and peripheral utilization of glucose is also influenced by increased secretion of insulin into the blood stream.
- Regenerating pancreatic β-cells resulting in increased synthesis and secretion of insulin into the blood stream.

CONCLUSIONS

Our studies indicate that both Ficus and Morus exhibit strong antidiabetic and anti-atherogenic effect and hence can be utilized as an adjunct in the management of type 2 diabetes mellitus.

However, much more research is needed before prescribing these as 'mainstream alternative therapies'

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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