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Potential hypoglycemic & hypolipidemic effect of *Morus Indica* and *Asystasia gangetica* in alloxan induced diabetes mellitus

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ABSTRACT

The present research was made to investigate the potential hypoglycemic and hypolipidemic effect of *Morus Indica and Asystasia gangetica* in alloxan induced diabetes mellitus. Diabetes was induced by alloxan (150 mg/kg i.p) into rats. Ethanolic extract of leaves of *Morus Indica and Asystasia gangetica* was administered to alloxan induced diabetic rats. Glibenclamide used as a reference standard. Blood glucose, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol and total proteins were estimated from the serum by using standard kits. All groups show significant increase in the level of biochemical parameters were decreased by administration of ethanolic extract of leaves of *Morus Indica and Asystasia gangetica.* From this study it has been concluded that the ethanolic extracts of leaves of *Morus Indica and Asystasia gangetica* having good hypoglycemic and hypolipidemic effect.

Keywords: *Morus Indica, Asystasia gangetica,* Alloxan, Diabetes mellitus, Hypolipidemic Effect.

INTRODUCTION

The Indian system of medicine has treated diabetes with its herbals for ages. Vegetables are among the numerous plant adjuncts tried for the treatment of diabetes mellitus. In recent years, there has been a renewed interest to screen such plant food materials, especially, to examine the long- term beneficial effect of dietary vegetables, to identify the active principle, and to understand the mechanism of action, which is at present unclear (Tierney et al., 1999). Liver is an insulin dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes (Seifter & England, 1982). During diabetes a profound alteration in the concentration and composition of lipid occurs (Sochar et al., 1995). Decreased glycolysis, impeded glycogenesis and increased gluconeogenesis are some of the changes of glucose metabolism in the diabetic liver. Diabetes mellitus is known to cause hyperlipidemia through various metabolic derangements. Among several metabolic derangements, insulin deficiency has been known to stimulate lipolysis in the adipose tissue and give rise to hyperlipidemia and fatty liver. Thus, in diabetes hypercholesterolemia and hypertriglyceridemia often occur (Hardman & Limberd, 2001).

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Many traditional plant treatments for diabetes are used throughout the world. Plant drugs (Bailey & Day, 1989) and herbal formulation (Mitra et al., 1996; Annapurna et al., 2001; Battacharya et al., 1997) are frequently considered to be less toxic and more free from side effects than synthetic one. Based on the WHO recommendations hypoglycemic agents of plant origin used in traditional medicine are important (WHO, 1980).

Morus indica (Mulberry tree) of the family Moraceae has been widely cultivated in countries all over the world including temperate to tropical areas. Different parts of the plant are used as herbal medicine for blood serum glucose reduction, cholesterol and lipids levels reduction, antiphlogistic, diuretic and expectorant effects.

Andallu and Varadacharyulu have reported antidiabetic activity of *Morus indica* in streptozotocin induced diabetes in rats (Andallu and Varadacharyulu, 2001).

Asystasia gangetica of family Acanthaceae has been claimed for anti asthmatic, anthelmentic and antidiabetic property (Akah et al., 2003).

Leaves are also widely used as food source, because it contains high amounts of proteins, amino acids, minerals and fibers (Yeoh and Wong, 1993). However, no scientific reports were available to support its antidiabetic activity.

The present investigation was undertaken to study the effect of the potential hypoglycemic & hypolipidemic effect of *Morus Indica* and *Asystasia gangetica* in alloxan induced diabetes mellitus.

MATERIAL AND METHODS

Drugs & Chemicals

Alloxan monohydrate was purchased from Sigma-Uldrich, USA. Glibenclamide was a gift from Cipla Ltd, India. All biochemical estimations were assayed by using kits from Span Diagnostics Ltd., India. All other biochemicals used in this experiment were purchased from Sigma-Uldrich, USA. The chemicals were analytical grade.

Experimental animals

Male Wistar rats of body wt. 180–200 g were obtained from central Animal House, Sri Padmavathi School of Pharmacy. The animals were fed on standard pellet diet (Hindustan Lever, Mumbai, India) and water ad libitum. The rats used in the present study were maintained in accordance with guidelines of the CPCSEA, India and the study approved by the ethical committee (1016/a/06/CPCSEA/006/2009).

Preparation of plant extract

Leaves of *Morus indica* & *Asystasia gangetica* were collected from the Rayachoty, Kadapa and Mudhumalai hills, Coimbatore. Their botanical identities were authenticated by Dr. Yashodamma, Department of Botany, Sri Ventateswara University, Tirupati. The shade dried leaves were powdered to get a course granule. About 250 g of dried powder of both were extracted with 90% and 70% ethanol respectively by continuous hot percolation, using soxhlet apparatus. The resulted dark – brown extract was concentrated up to 100 ml on Rota vapour under reduced pressure. The concentrated crude extracts were lyophilized in to powder and used for the study.

Phytochemical screening

The alcoholic extracts obtained were subjected to preliminary phytochemical screening, to identify the chemical constituents. The methods of analysis employed were those described by (Harbone & Baxter, 1993; Trease & Evans, 1983).

Experimental induction of diabetes in rats

The rats were injected intraperitoneally with alloxan monohydrate dissolved in sterile normal saline at a dose of 150 mg/kg body wt (Katsumata et al., 1999). After 2 weeks, rats with moderate diabetes having glycosuria (indicated by Benedict's qualitative test) and hyperglycemia (i.e. with a blood glucose of 200–300 mg/dl) were used for the experiment.

Experimental design

The rats were divided into six groups of six rats each after the induction of alloxan diabetes. Group1: Normal treated rats. Group2: Diabetic control rats. Group 3: Diabetic rats given aqueous solution of glibenclamide (500 µg/kg, p.o.) for 28 days. Group 4: Diabetic rats given extract of *Asystasia gangetica* (100 mg /kg, p.o.) for 28 days. Group 5: Diabetic rats given extract of *Morus indica* (400 mg /kg, p.o.) for 28 days. Group 6: Diabetic rats given extract of *Morus indica* (400 mg /kg, p.o.) in combine with the extract of *Asystasia gangetica* (100 mg /kg, p.o.) for 28 days. The blood samples were drawn on 7th, 14th, 21st and 28 th day from the retro orbital venous plexus of rats under ether anesthesia using a glass capillary tube after a fast of 12 hrs and the blood was centrifuged (2,500 rpm/10min) to get serum. The serum was used for biochemical estimation of blood glucose, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol and total proteins. After 28 days the rats were sacrificed, pancreas and liver were harvested and immediately frozen in liquid nitrogen for biochemical estimation.

Biochemical parameters

Blood glucose, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol and total proteins were estimated from the serum by using standard kits (Lopes-Virella et al., 1977; McGowan et al., 1983; Lowry et al., 1951).

Statistical analysis

The data for various biochemical parameters were analyzed using analysis of variance (ANOVA) and the group means were compared by Turkey-Kramer Test (GraphPad V-3.06). Values was considered statistically significant when at $p < 0.05$.

RESULTS

Phytochemical screening

Phytochemical screening of both the plant extracts revealed that the presence of flavonoids, alkaloids,

Table 1. Effect of *Asystasia gangetica & Morus indica* on serum glucose levels in diabetic rats.

Group	Treatment	Serum glucose (mg/dl) (Mean±SEM)				
		0th day	7th day	14th day	21st day	28th day
I	Normal	62.40±6.45	96.70±6.45	86.80±5.45	78.57±5.97	61.70±5.45
II	Control	224.70±16.56	194.00±16.46 [a]	207.80±16.26 [a]	211.60±16.85 [a]	232.30±18.44 [a]
III	Standard	176.6±16.45	113.75±6.65 [b]	98.18±10.74 [b]	92.00±7.26 [b]	88.56±9.47 [b]
IV	AGLE	216.20±18.44	102.68±8.78 [b]	99.06±6.88 [b]	93.07±8.95 [b]	89.00±6.25 [b]
V	MILE	224.00±19.50	78.87±5.49 [b]	73.43±8.35 [b]	78.22±10.49 [b]	74.23±6.38 [b]
VI	AGLE+MILE	228.80±19.25	91.62±7.55 [b]	67.34±6.45 [b]	62.12±6.46 [b]	61.34±5.45 [b]

a = $p < 0.001$, when compared to normal. (G-I), b = $p < 0.001$, when compared to control. (G-II)

glycoside, tannins, saponins, phytosterols.

Effect of *Asystasia gangetica & Morus indica* on serum glucose levels in diabetic rats

In animals treated with alloxan (G-I) (150 mg/kg i.p) a significant increase in the serum glucose levels was observed on the 7th, 14 th, 21st and 28th day, when compared to the normal group (G-I). Group-III treated with standard drug (glibenclamide – 0.5 mg/kg p.o) showed a significant decrease in serum glucose levels on 7th, 14th, 21st and 28th day, when compared to the diabetic control group (G-II). On administration of *Asystasia gangetica & Morus indica* leaf extracts alone and in combination groups (G-III, IV and V), the blood glucose levels were decreased on7th, 14th, 21st and 28th day, when compared to the control group (G-II) (Table 1).

Effect of *Asystasia gangetica & Morus indica* on serum triglyceride levels

Group –II animals receiving alloxan showed a significant increase in triglyceride levels on 14th, 21st and 28th day when compared to the normal group (G-I). Rats treated with standard drug (G-III) had significantly lowered triglyceride level on 14 th, 21st and 28th day when compared to the control group (G-II). A significant decrease in serum triglycerides was observed in animals treated with *Asystasia gangetica & Morus indica* leaf extracts alone and in combination(G-III,G-IV and G-V), when compared to the control group(G-II) (Table 2).

Table 2. Effect of *Asystasia gangetica & Morus indica* on serum triglyceride levels in diabetic rats.

Group	Treatment	Serum triglyceride (mg /dL) (Mean ± SEM) on				
		0th day	7th day	14th day	21st day	28th day
I	Normal	148.30±12.44	150.20±16.45	148.00±16.44	159.21±16.83	149.80±15.48
II	Control	190.40±17.45	204.00±18.48	219.00±16.15[a]	231.00±16.25[a]	244.00±17.23[b]
III	Standard	184.00±14.55	186.10±15.11	180.80±13.09[c]	176.91±19.07[c]	164.10±17.03[e]
IV	AGLE	174.00±14.32	177.20±16.42	172.30±14.45[c]	176.20±18.99[c]	166.40±14.42[e]
V	MILE	172.60±13.40	171.90±16.45	182.70±12.08[c]	170.50±14.38[d]	168.00±15.86[e]
VI	AGLE+MILE	172.30±13.64	174.20±15.44	170.89±17.48[c]	170.30±14.50[d]	169.30±16.47[d]

a= p< 0.01, when compared to normal (Group-I), b=p<0.001, when compared to normal (Group-I), c=p<0.05, when compared to control (Group-II), d= p<0.01, when compared to control (Group-II), e=p<0.001, when compared to Control (Group-II).

Table 3. Effect of *Asystasia gangetica & Morus indica* on serum cholesterol in diabetic rats.

Group	Treatment	Serum cholesterol (mg /dl) (Mean ± SEM) on				
		0th day	7th day	14th day	21st day	28th day
I	Normal	57.68±6.51	063.00±6.45	52.00±6.45	59.00±6.45	61.00±6.45
II	Control	146.60±12.45	154.00±13.32	168.0±16.12[a]	161.0±16.40[a]	159.0±16.25[a]
III	Standard	180.00±16.46	079.00±7.20	81.00±7.14[b]	68.00±5.22[b]	70.00±5.05[b]
IV	AGLE	129.80±9.45	110.00±5.23	84.00±6.45[b]	89.00±7.46[b]	86.00±6.25[b]
V	MILE	141.70±11.25	109.00±6.30	87.00±7.04[b]	83.00±6.35[b]	79.00±7.85[b]
VI	AGLE+MILE	123.70±12.47	91.00±5.95	77.50±5.28[b]	71.00±6.26[b]	69.00±8.45[b]

a = p < 0.001, when compared to normal. (G-I), b= p < 0.001, when compared to control. (G-II)

Table 4. Effect of *Asystasia gangetica & Morus indica* on serum HDL level in diabetic rats.

Group	Treatment	Serum HDL (mg /dl) (Mean ± SEM) on				
		0th day	7th day	14th day	21st day	28th day
I	Normal	54.40± 5.54	47.50±5.57	57.73± 5.00	49.70± 5.56	51.30±5.54
II	Control	49.70±5.56	47.20± 8.72	41.40±4.48[a]	37.20± 3.60[a]	31.23± 3.58[b]
III	Standard	51.35±5.68	57.53±5.56	59.40± 4.56[c]	56.30±5.55[d]	57.63±5.55[d]
IV	AGLE	58.93±4.74	51.53± 7.69	60.30±5.05[c]	73.63± 6.69[d]	61.30±6.64[d]
V	MILE	42.63±4.90	58.70± 6.85	69.99± 4.02[d]	72.58±6.50[d]	71.42± 5.58[d]
VI	AGLE+MILE	57.40± 5.59	47.60± 5.57	61.30± 5.00[c]	59.32±5.47[c]	57.70± 8.51[c]

a =p < 0.05, when compared to normal. (G-I), b =p < 0.001, when compared to normal. (G-I), c =p < 0.01, when compared to control (G-II), d =p< 0.001, when compared to control. (G-II)

Effect of *Asystasia gangetica & Morus indica* on serum cholesterol

The biochemical parameter, serum cholesterol has shown significant increase in alloxan induced group (G-

Table 5. Effect of *Asystasia gangetica & Morus indica* on serum LDL levels in diabetic rats.

Group	Treatment	Serum LDL (mg /dl) (Mean ± SEM) on				
		0th day	7th day	14th day	21st day	28th day
I	Normal	43.20± 6.39	52.10± 6.43	48.00±6.45	54.40±6.45	53.00± 6.45
II	Control	102.0±16.45	105.00±14.45	108.10±12.43[a]	114.20±13.47[a]	118.00±11.45[a]
III	Standard	65.17±6.46	62.00±6.45	63.20±6.46[b]	61.00±6.85[c]	60.00± 5.25[c]
IV	AGLE	78.40±6.45	82.10±7.44	70.21±4.10[b]	72.10±5.50[b]	71.00±6.45[c]
V	MILE	73.40±7.48	74.00±5.26	80.30±4.46[c]	73.30± 5.80[b]	72.30±7.45[c]
VI	AGLE+MILE	62.10±6.49	68.30±6.49	62.00±6.45[c]	66.27± 5.93[c]	61.00± 6.58[c]

a =p < 0.001, when compared to normal. (G-I), b =p < 0.01, when compared to control. (G-II), c =p < 0.001, when compared to control. (G-II)

II) when compared with the normal group (G-I). A significant decrease in the levels of serum cholesterol was observed from 14th day onwards on administration of glibenclamide (G-III), when compared with the control group (G-II). The *Asystasia gangetica & Morus indica* leaf extracts alone and in combination (G-III, G-IV and G-V) caused a significant decrease in the serum cholesterol levels from the 14th day onwards, when compared to the control group (G-II) (Table 3).

Table 6. Effect of *Asystasia gangetica & Morus indica* on serum proteins level in diabetic rats.

Group	Treatment	Serum proteins (mg /dl) (Mean ± SEM) on				
		0th day	7th day	14th day	21st day	28th day
I	Normal	8.89±1.62	6.32± 0.83	8.63± 0.70	8.90± 0.89	9.01± 1.61
II	Control	6.30±.0.91	5.01± 0.65	4.69±0.67[b]	4.50± 0.76[a]	3.30±0.75[b]
III	Standard	5.70±1.02	5.46±0.91	6.79±0.69[c]	6.85± 0.92[c]	7.85± 0.92[e]
IV	AGLE	6.23±0.80	6.97±0.62	7.89±0.78[d]	8.08±1.00[d]	7.90± 0.78[e]
V	MILE	6.36±0.63	6.01± 0.74	8.29±0.89[e]	8.59±1.16[e]	8.60± 1.0[e]
VI	AGLE+MILE	6.74±0.87	6.00± 0.81	7.90±0.65[e]	8.18±0.81[e]	8.18±0.91[e]

a =p <0.05, when compared to normal. (G-I), b =p <0.001, when compared to normal. (G-I), c =p <0.05, when compared to control. (G-II), d = p<0.01, when compared to control. (G-II), e =p <0.001 when compared to control. (G-II).

Effect of *Asystasia gangetica & Morus indica* on serum HDL level

The rats induced with alloxan(G-II) a significant decrease in HDL levels was observed on 14th, 21st and 28th day,when compared to the normal group(G-I). Group-III,receiving standard drug (glibenclamide-0.5 mg/kg p.o) showed a significant increase in HDL levels on14th, 21st and 28th day , when compared to the control group (G-II). Administration of *Asystasia gangetica & Morus indica* leaf extracts both alone and in combination (G-III, G-IV and G-V) have shown a significant increase in HDL levels on 14th ,21st and 28th day, when compared to control group (G-II) (Table 4).

Effect of *Asystasia gangetica & Morus indica* on serum LDL levels

Alloxan causes significant increase in LDL levels of control group (G-II) when compared with normal group (G-I). Standard drug glibenclamide significantly decreased LDL levels from 14th day onwards, when compared with the control group (G-II) (Table 5). Leaf extracts of *Asystasia gangetica & Morus indica* at the doses of 100 mg/kg and 400 mg/kg alone and in combination, significantly decreased LDL levels on 14th, 21st and 28th day, when compared to control group (G-II).

Effect of *Asystasia gangetica & Morus indica* on serum proteins level

Serum total proteins levels were decreased in control group (G-II) on administration of alloxan, when compared to the normal group (G-I). Treatment with standard drug (glibenclamide) improves serum protein levels approximately near to normal group (G-I), when compared with the control group (G-II). Administration of plant extracts (G-III, G-IV and G-V) alone and in combination significantly increased the serum protein levels, when compared to the control group (G-II) (Table 6).

DISCUSSION

Diabetes mellitus is one of the leading causes of death, illness and economic loss all over the world. Insulin-dependent (Type I, IDDM) diabetes is characterized by juvenile onset and by absolute insulin deficiency. Non-insulin-dependent (Type II, NIDDM) diabetes is characterized by mature onset, by varying basal insulin levels and a frequent association with obesity. It is likely that further heterogeneity exists within these two basic types. Similarly, animal models of diabetes differ significantly from each other and none of them can be tak-

en, without reservations, to reproduce the essentials of human diabetes (Bell and Hye, 1983).

Experimental diabetes has the advantage that it allows the analysis of the biochemical, hormonal and morphological events that take place not only during the induction of a diabetic state but also after it has taken place and during its evolution to a severe insulin deficiency or even death. This strategy has great advantages but it has to be considered that none of animal models with induced diabetes corresponds exactly to the human type-2 diabetic mellitus, nonetheless they provide models to investigate the pathogenic mechanism that lead to hyperglycemia and its consequences (Bailey et al., 1997).

Alloxan became the first diabetogenic chemical agent when Dunn and Letchie accidentally produced islet-cell necrosis in rabbits while researching the nephrotoxicity of uric acid derivatives. Alloxan is a specific toxic substance that destroys the β cells provoking a state of primary deficiency of insulin without affecting other islet types (Dunn et al., 1943; Goldener & Gomori, 1964). Hence, alloxan was selected to induce diabetes in the present study.

Currently available drugs for treatment of Diabetes mellitus have a number of limitations, such as adverse effects and high rate of secondary failure (Koski, 2004). As there is a growing trend towards using natural remedies as adjuncts to conventional therapy, traditionally used plants might provide a useful source of new hypoglycemic compounds (Bailey and Day, 1989). Although *Asystasia gangetica* is described as a medicinal plant being used for various purposes, no scientific reports exist on its antihyperglycemic, antihyperlipidemic and antioxidant properties. The present study demonstrated for the first time the antihyperglycemic, antihyperlipidemic and antioxidant properties of *Asystasia gangetica*.

The extracts of *Morus indica* have been reported to possess medicinal properties, including hypoglycemic, hypotensive and diuretic activities (Andallu and Varadacharyulu, 2001). The hypoglycemic and antioxidant effect of mulberry leaves or shoot culture extract has been demonstrated using streptozotocin induced diabetic animals (Andallu and Varadacharyulu, 2001; Kelkar et al., 1996). Although the importance of the hypoglycemic activity of mulberry leaves has been recognized, its effect in combination with other herbs like *Costus igneus* also investigated (Urooj & Devi, 2008). Therefore, the present study was designed to investigate the effect of mulberry leaves in combine with *Asystasia gangetica* against alloxan induced diabetes.

A number of plants have been reported to possess hypoglycemic effects and the possible mechanism suggested for such hypoglycemic actions could be through an increased insulin secretion from β-cells of islets of Langerhans or its release from bound insulin or such hypoglycemic effects of plant extracts could also be because of their insulin-like actions.(Twaij and Badr., 1988; Kasiviswanath et al., 2005) Similar mechanisms may be considered responsible for the hypoglycemic action shown by *Asystasia gangetica & Morus indica* alone and in combination in diabetic rats.

The abnormally high concentration of plasma and hepatic lipids in diabetes is mainly due to an increase in the mobilization of free fatty acids from the peripheral depots, since insulin inhibits hormone sensitive lipase (Al-Shamony et al., 1994).The marked hyperlipidemia that characterizes the diabetic state is regarded as a consequence of the uninhibited actions of lipolytic hormones (glucagon and catecholamines) on the fat depots (Ravi et al., 2005). On the other hand, increased LDL-cholesterol may arise from glycosylation of the lysyl residues of apoprotein B (Ravi et al., 2005). The ability of LDL-cholesterol to form lipid peroxides was found to be specifically responsible for the atherogenesis in diabetic patients (Kondo et al., 2001). It is reported that a deficiency in lipoprotein lipase activity in diabetics may contribute to significant elevation of triglycerides in blood and with insulin administration; lipoprotein lipase activity is elevated and leads to lowering of plasma triglyceride concentrations (Lopes-Virella et al., 1983; Braun and Severson, 1992). The *Asystasia gangetica & Morus indica* administration almost reversed these effects as it reduced total cholesterol and triglyceride concentrations (plasma), LDL concentration and increased HDL notably in combination. In this context, combination of *Asystasia gangetica & Morus indica* was found to be as effective as glibenclamide in reducing the plasma lipid profiles in diabetic rats.

ABBREVIATIONS

AGLE – *Asystasia gangetica* leaf extract , MILE – *Morus indica* leaf extract, LDL – Low density lipoprotein, HDL – High density lipoprotein.

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