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Research Article

EFFECT OF METHONOLIC FRUIT PERICARP EXTRACT OF *GARCINIAINDICA*ONHYPERCHOLESTREMIC OF DIABETIC RATS INDUCED WITH ALLOXANE

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ABSTRACT

Our aim was to evaluate the antihyperglycemic and antihypercholestremic effect of methanolic extract of *Garciniaindica*(MEGI)(Guttiferae) fruits on alloxan induced diabetic rats. Garcinia is a rich source of bioactive molecules including xanthones, flavonoids, benzophenones, lactones and phenolic acids. Blood glucose, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol levels in serum, pancreas, liver and kidney were determined by specific colorimetric methods. The levels of pancreas enzymatic and nonenzymaticantioxidant enzymes (catalase, lipid peroxidation and reduced glutathione) were observed. An increase in blood glucose was accompanied by an increase in total cholesterol, triglycerides, decreased in HDL choleterol in diabetic rats. Thelevels ofpancreas enzymatic and non-enzymatic antioxidant enzymes (catalase, lipid peroxidation and reduced glutathione) weresignificantly bring back to normal. Our results thus suggested that the "*Garciniaindica*" could be used as a safe alternative antihyperglycemic, antihyerlipidemic drug for diabetic patients.

Keywords: *GarciniaIndica,* Serum Glucose, Triglycerides.

1. INTRODUCTION

Inherited and/or acquired deficiency in the production of insulin by pancreas or the ineffectiveness of the insulin produced, causes diabetes mellitus. Contributory factor in the pathogenesis of diabetes also comprises of oxidative stress (Murugan P et al., 2006). Protein glycation and glucose autoxidation generates free radicals in diabetic patients, which in turn catalyses lipid peroxidation (Onorato JM et al., 2000).Hyperlipidemic condition is metabolic complication of both clinical and experimental diabetes (Gandhi HR, 2001). Low density lipoprotein in diabetic patients leads to abnormal metabolism and is associated with increase in very low density lipoprotein (VLDL) secretion and impaired VLDL catabolism. Ultimately, this leads to atherosclerotic plaque formation. Patients with diabetic mellitus are more likely to develop microvascular and macrovascular complications than the non diabetic population.

The action of alloxan in the pancreas is preceded by its rapid uptake by the insulin-secreting cells (β-cells) (Heikkila et al., 1976), and also due to autoimmune destruction of the β-cells of the pancreas (Atkinson and Maclaren, 1994). Over the years, various medicinal plants and their extracts have been reported to be effective in the treatment of diabetes (Marles and Fransworth, 1995). Plants are rich sources of antidiabetic, antihyperlipedemic and antioxidant agents such as flavonoids, gallotannins, amino acids and other related polyphenols (Muruganandan et al., 2005; Miyake et al., 2006). Numerous plants have been reported to possess hypoglycemic activity (Bailey and Day, 1989; Handa, 1991; Ivory, 1989; Swanston-Flatt, 1989, 1990; Nagaraju and Rao, 1990; Rastogi and Mehrotra, 1993; Marles and Farnsworth, 1994).

Garciniaindica, also known as kokum, is a plant native to tropical Asian, African and polynesian countries (Chandran, 1996). Kokum is an underexploited fruit tree species found in tropical rain forests of Western Ghats of India, Konkan, North Kanara, South Kanara, Bombay, and Goa (ChaudhuryR, 2005; Cooke T, 1967). The extract obtained from *Garciniaindica* fruits is an herbal preparation that has been reported to have many medicinal compounds like citric acid, malic acid, polyphenols, carbohydrates (Cardenas, 1990), ascorbic acid (Peter, 2001), flavonids and Phenolic acids (patil, 2005), anthocyanin pigments (Nayak, 2006; Peter, 2001), polyisoprenylatedbenzophenones, Camboginol and isoxanthochymol (Sunil K, 2009). There are no reports in literature concerning the anti-hyperglycemic potential of *Garciniaindica* of the oral administration of methanolic extract on serum glucose levels in diabetic rats.

2. MATERIALS AND METHODS

2.1 Plant material

Fresh kokum (*Garciniaindica*) fruits were procured from the orchards near Mangalore in the month of April 2009 and identified and authentifiedby Botanical Science of India, Coimbatore, and Tamil Nadu.

2.2 Preparation of photochemical extract

The fresh fruits are washed and cut into four equal pieces (runds) parallel to the major axis, then ground after the removal of seeds. Then pericarp were dried under sunshade for 6-7 days and coarsely powdered. The powder was extracted using soxhelt apparatus with methanol 2000ml.The methanol was distilled condensed using rotatory evaporator and stored in desicator. The powder of the extract was suspended in appropriate solvent system.

2.3 Chemicals

Alloxane was procured from Sigma Co. USA, glibenclamide from USV Limited, Maharashtra, while other chemicals used were of analytical grade obtained from E. Merck and Hi-media, India.

2.4 Animals and treatment

Male Wistar rats (140–170 gm) were used. These were bred in our animal facility and housed in an air-conditioned room (approximately 22°C) with controlled lighting 12:12 h light/dark cycle. The animals were maintained with pelleted, while tap water was available ad libitum. The study has got the clearance from the Institutional Animal Ethical Committee (IAEC) the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Rats were acclimatized to the environment for 15 days prior to the experiment; animals were divided into five groups. Each group contains 6 rats. Fasted animals were deprived of food for at least 16 hr but allowed free access to water.

2.5 Induction of diabetes

Diabetes was induced by injection of a single intra-peritoneal dose of Alloxan monohydrate (freshly prepared in 0.1% normal saline). Overnight fasted rats were injected with Alloxan (alloxan; 120 mg/kg body wt., *i.p*) to induce diabetes. Diabetic was confirmed by glucose estimation. Animal with plasma glucose level > 200 mg / dl were selected for the study. Diabetic induced Animals were grouped for further study. After 3 days of alloxan induction, treatment was started.

2.6 Grouping of animals

Fasting blood was collected for blood glucose estimation before starting the treatment on the first day. The first group was used as control and received H_2O as vehicle. The second group received a single dose of and was divided into four subgroups after establishing of the diabetes for 1 week. The first group was kept as a normal control, second groups as disease control, while the third and fourth groups received orally 1.0 ml of glibenclmide(25mg/kg,b.wt), MEGI (200 mg/ kg) and MEGI (400 mg /kg)respectively by gastric intubation daily for 28 days. Blood was collected from retro orbital plexus. All five groups were sacrificed on the 28th day in fasting condition by cervical dislocation and then blood was collected for various biochemical estimations. Pancreas, liver and kidney were collected for estimation of tissue lipids and other enzymatic and non enzymatic parameters.

2.7 Biochemical Estimations

Fasting blood glucose levels were estimated by GOD-POD method as described by Trinder, 1975. Serum cholesterol and triglyceride (TG) levels were measured using standard methods (Hyvarinen, 1962; Zlatkis, 1953; Foster, 1973) and HDL-cholesterol (Gidez, 1950),Liver and kidney samples from animals were weighed and homogenized using appropriate buffer in an all glass homogenizer with Teflon pestle using specified medium and then used for biochemical estimations. We have used specific manual methods to evaluate the levels of glucose and lipids. Lipids in the pancreas, kideny and Liver (Folch, 1957).

2.8 Catalase Estimation

The activity of catalase was assayed according to the method of Takahara S et al., 1960. Phosphate buffer (1.2 mL) and 0.2mL of tissue homogenate were mixed, and the reaction was started by the addition of 1.0mL of H2O2 solution. Decrease in the absorbance wasmeasured at 240 nmat 30 sec intervals for 3min. For the enzyme blank, distilled water was used instead of hydrogen peroxide. The activity of enzymewas expressed as μmoles of H_2O_2decomposed/min/mg of protein.

2.9 Lipid peroxidation assay

The levels of lipid peroxidation in the pancreatic tissues were measured as malondialdehyde (MDA) according to the method of Ohkawa et al., 1979. To 0.1 ml pancreatic homogenate, 0.2 ml of 8.1% (w/v) sodium dodecyl sulphate (SDS), 1.5 ml of 20% (v/v) glacial acetic acid (pH 3.5) and 1.5 ml of 0.8% (w/v) thiobarbituric acid (TBA) were added. The mixture was made up to 4 ml with the addition of 0.7ml of distilled water. The test tubes were heated at 95^{o}C for an hour with a marble on top of each test tube. After incubation, the test tubes were cooled and then centrifuged at 3000 × g for 10 minutes. After centrifugation, the concentrations of MDA were measured spectrophotometrically at 532 nm. 1,1,3,3- tetraethoxypropane (TEP) was used as standard. The MDA levels were expressed as nmol per mg protein.

2.10 Reduced Glutathione Assay (GSH)

Reduced glutathione was determined by the method
of Sedlak and Lindsay (Sedlak J, 1968) 0.5mL tissue homogenate was mixed with 0.2M Tris buffer with pH of 8.2, and then contents\ were mixed with 0.1mL of 0.01M Ellman's reagent, (5,5'- dithiobis-(2-nitro-benzoic acid)) (DTNB), then centrifuged at 3000 g for 15 min. The absorbance was read at 412 nm. A series of standards treated in a similar way also run to determine the glutathione content. The amount of glutathione is expressed as mg/100 g of tissue.

Statistical analysis

Values are mean±SEM for six rats in each group, and significance of the differences between mean values was determined byBonferroni-post test.The levels of significance were evaluated with p values.

3. RESULTS AND DISCUSSION

Over the years, various medicinal plants and their extracts have been reported to be effective in the treatment of diabetes (Marles, 1995).Plants may act on blood glucose through different mechanisms, some of them may have insulin like substances and some may inhibit insulinase activity(Bopanna, 1997). Some plants are involved in the stimulation of cells to produce more insulin (Chang, 1980; Collier, 1987) and others may increase cells in the pancreas by activating regeneration of pancreatic cells(Chakravarthy, 1980).Pancreatic β-cells are particularly susceptible to the deleterious effects of ROS because of their low expression of the antioxidant enzymes genes as compared to other tissues (Lenzen S, 1996, Zhang H, 1995). Hence, the cellular antioxidant status is an important determinant of its susceptibility to oxidative damage.

The diabetogenic agent alloxane is a hydrophilic and chemicallyunstable pyrimidine derivative, which is toxic to pancreatic β-cellsbecause it can generate toxic free oxygen radicals during redoxcycling in the presence of reducing agents such as glutathione andcysteine (Szkudelski, 2001). The increase in oxygen free radicals indiabetes could be due to increase in blood glucose levels, whichgenerates free radicals due to autooxidation(Yadav, 2000).

In a sub-chronic antidiabetic study, it was observed that prior to the extract administration there were no significant differences between the fasting blood glucose levels of the diabetic groups of animals. However, after four weeks, the fasting blood glucose levels of the treated rats were significantly lower than the diabetic controls. In contrast, the blood glucose level of the untreated diabetic rat remained elevated throughout the experimental period. The results were presented in Table 1.

Diabetes-induced hyperlipidemia is attributable to the excess mobilization of fat from the adipose tissue due to the under utilization of glucose. The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of free fatty acids from the peripheral depots since insulin inhibits the hormone sensitive lipase.In the present study MEGI of a dose of 400 mg/kg b.wt significantly reduced total cholesterol, VLDL, LDL and triglycerides while at the same time significantly increased the HDL levels in serum of alloxaneinduced diabetic rats. The total lipid profile in serum (TG, TC, LDL, VLDL and fall of HDL) of the alloxane induced diabetes animals treated with MEGI (MEGI 200mg/kg, b.wt or MEGI 400 mg/kg, b.wt) was substantially improved, as compared to diabetic control group. MEGI was also decreases the lipid content in the organs like pancreas, kidney and liver (graph 3,4 &5). The strong anti-

hyperglycemic effect of MEGI could indirectly be related to beneficial action against the abnormal high concentration of serum lipids observed in diabetes animals. In the present study treatment with the MPGI showed reversing effect of serum, pancreas, liver and kidney lipid levels in alloxane treated diabetic rats.

Various tissues are more prone to oxidative damage and could result in various complications in long-term diabetes, implying that, the restoration of antioxidant status is an important parameter to evaluate the effect of antidiabetic compound.In the present work, involvement of free radicals in progressionof disease and protective effects of MPGI has been examined in pancreas, liver and kidney.The catalase in *vivo* antioxidant is present in almost all the mammalian cells and protects the cell from oxidative damage by H_2O_2 and hydroxyl radical. The levels of catalase were found to decrease in diabetic condition but the treatment with MPGI significantly elevates the catalase levels in alloxane induced diabetic rats. The lipid peroxidation and antioxidant potential have been measured in pancreas, liver and kidney tissues of control and experimental groups of rats. The tissue lipid peroxidation in diabetic rats was increased, which might be due to an increase in the level of blood glucose(Manna P, 2010).Elevation of LPO is attributed to the enhanced production ofreactive oxygen species. This increased lipid peroxides formation during diabetes disturbs theanatomical integrity of the membrane leading to the inhibition of several membrane bound enzymes (Jamme I et al., 1995). Theresults revealed a sharp decreased level of MDA in diabetic rats treated with MPGI and glibenclamidewhen compared to untreated diabetic rats indicating the efficacy of treatment.In the present study, we observed aMDA formation, the index of lipid peroxidation, was significantlyincreased in alloxanetreated diabetic rats.Treatment with MPGI significantly reduced MDA level as shown in table 2.

The GSH is the most important intracellular thiol antioxidant and a major determinant of the intracellular redox status. Intracellular GSH levels and GSH redox status play a centralrole in regulating a wide variety of cell responses, including signal transduction, immune regulation, maintenance of protein structure cell proliferation, and apoptosis.GSH protect the cellular system against the toxic effects of lipidperoxidation. A marked depletion in the GSH content a liver wasobserved in diabetic control rats. Furthermore, treatment withMPGI showed a significant restoration in GSH content in the tissues pancreas, liver and kidney of diabeticrats (Table 2).The decreased activities of theseenzymes may be due to the production of reactive oxygen species(ROS) such of superoxide (O2−•), hydrogen peroxide (H_2O_2), andhydroxyl radical (OH) that reduces the activity of these enzymes(Kaleem, 2005; Vincent, 2004).

The protective activity offered by the MPGI was might be due to the presence of active constituents like citric acid, malic acid, polyphenols, carbohydrates (Cardenas, 1990; Yoshikawa, 2000), ascorbic acid (Peter, 2001), flavonids and Phenolic acids (patil, 2005), anthocyanin pigments (Nayak, 2006; Peter, 2001; Chetan, 2009).

CONCLUSION

It was concluded that reduced hyperglycemia and associated oxidative stress in alloxaneinduced diabetic rats, decreased glucose level, decreased hypercholestremic condition and increased antioxidants markers including enzymatic and nonenzymatic antioxidants. Thus, the present study has shown that *Garciniaindica*has a pancreas, liver and kidney protective nature against alloxaneinduced diabetic experimental rats due to decreasing the levels of oxidative markers and improvement of antioxidants systems.

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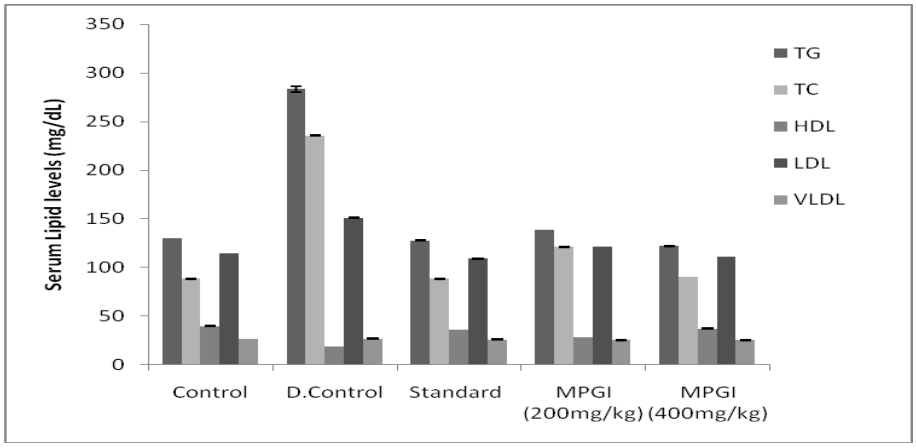
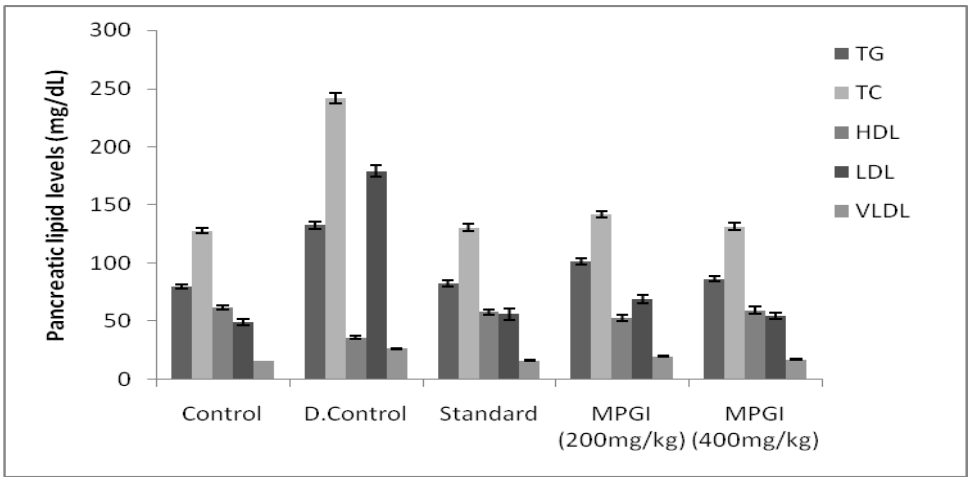
Table 1: Effect of MPGI on serum glucose levels

Treatment (mg/kg)	0day	7day	14day	21day	28day
Control	112.66±0.71	96.16±1.19 ns	95.66±1.20 ns	101.33±1.97 ns	96.83±0.79 ns
D.Control	307±3.93	319.00±4.50 ns	324.33±5.66 ns	311.81±5.19 ns	302.83±6.11 ns
Standard	305.66±6.53	209.83±2.18*	129±1.18#	111.83±0.88$	92.50±0.99$
MPGI (200mg/kg)	307.88±199	211.83±1.22*	137.16±0.60#	109.33±0.49$	98.60±0.66$
MPGI (400mg/kg)	293.33±0.88	198.66±1.14#	123.33±1.84#	93.33±1.76$	88.23±0.51$

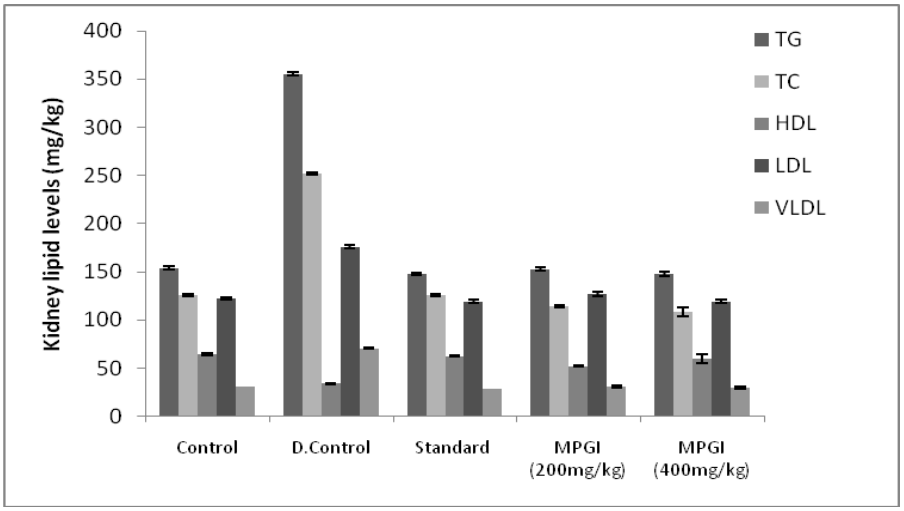
Results are expressed as mean±SEM, n=6, p<0.005. All 0 day are compared with 28 day using Two way ANOVA followed by Bonferroni-post test.*p> 0.05, #p<0.05, $p < 0.01



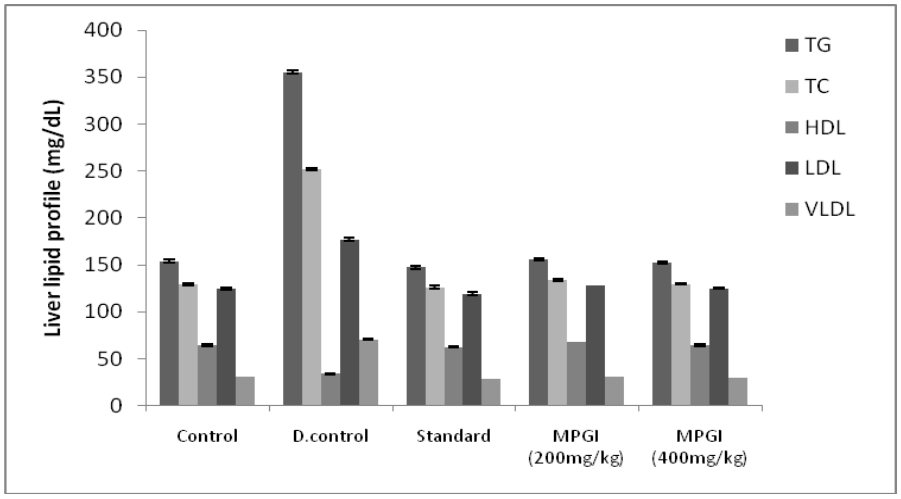
Graph. 1: Effect of *MPGI* on serum lipid levels



Graph. 2: Effect of *MPGI* on lipid levels in the pancreas



Graph. 3: Effect of *MPGI* on lipid levels in the Kidney



Graph. 4: Effect of *MPGI* on lipid levels in the liver

Table 2: Effect of *MPGI* on different parameters in pancreas, kidney and liver:

Treatment	MDA (nmol/gm of tissue)			GSH (mg/100g tissue)			CAT (U/mg of protein)		
	Pancreas	Kidney	Liver	Pancreas	Kidney	Liver	Pancreas	Kidney	Liver
Control	26.08±1.65#	123.96±0.88$	186.91±1.77$	17.99±1.98#	21.47±0.65$	45.21±3.85$	26.98±1.96$	35.95±1.86$	77.89±2.89$
D.control	63.96±1.02	256.98±1.36	340.75±1.36	10.65±2.61	15.18±0.14	20.98±2.06	15.96±1.45	18.76±1.34	29.61±1.87
Standard	34.95±0.98$	149.36±1.77$	276.95±0.53$	21.96±0.96$	21.38±0.32$	39.78±1.45$	26.89±0.73$	31.95±0.68$	62.78±0.79$
MPGI (200mg/kg)	42.56±0.75#	210.85±2.06*	319.84±2.46#	18.18±0.84#	20.11±0.30#	28.49±0.63#	20.66±1.32#	29.89±0.97$	56.96±2.41$
MPGI (400mg/kg)	29.45±1.23$	153.92±0.76$	284.66±1.86$	21.42±1.56$	22.17±0.38$	35.79±1.71$	27.23±2.13$	30.56±1.35$	68.44±0.69$

Results are expressed as mean±SEM, n=6, p<0.005. All the groups are compared with diseased group using Two way ANOVA followed by Bonferroni-post test. *p> 0.05, #p<0.05, $p < 0.01

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