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Full Length Article

α-Mangostin Mediated Pharmacological Modulation of Hepatic Carbohydrate Metabolism in Diabetes Induced Wistar Rat

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ABSTRACT

Garcinia mangostana L. (Fruit) has been commonly used as folklore drug in the treatment of various types of diseases. The present experiment was designed to evaluate the potential effect of α-mangostin mediated pharmacological modulation of hepatic carbohydrate metabolism in streptozotocin (STZ) induced diabetic rats. Oral glucose tolerance test (OGTT)

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β cells

was performed in normoglycemic rats. Single intraperitoneal injection of STZ (60 mg/kg, body weight) was used for induction the diabetes in Swiss albino (Wistar strain) rats. The rats were divided into different groups. Blood glucose level, body weight, insulin, glycated hemoglobin and hemoglobin levels were recorded at regular intervals. Biochemical parameters, liver enzymes, lipid profile, antioxidant parameters and inflammatory cytokine mediators were also scrutinized. Histopathology study of kidney, pancreas and liver were performed. The result of OGTT study depicted the better utilization of glucose in experimental rats. STZ induced diabetic rats treated with α-mangostin (25, 50 and 100 mg/kg, p.o.) and glibenclamide depicted the decline in the level of blood glucose; enhanced body weight and showed the better utilization of glucose by different organs. STZ induced diabetic rats treated with α-mangostin illustrated the increased level of plasma insulin, hemoglobin, hexokinase, HDL, total protein, SOD, CAT, GSH and declined level of glycated hemoglobin, fructose-1-6-biphosphatase, glucose-6-Phosphatase, TC, TG, LDL, VLDL, CRE, BUN, SGOT, SGPT, ALP and LPO at effective dose dependent manners. Histological study showed the inflamed blood vessels in diabetic kidney, which was less in α-mangostin treated rats; diabetic pancreatic showed the complete damage of β cells, islets, aciini and producing necrosis, but all damage was less obvious in α-mangostin treating group rats; diabetic liver showed the damage of hepatocytes as well as central vein but was less in treated groups. Considering the above results, α-mangostin shows potential to develop a medicine for diabetes, hyperlipidemia, renal and hepatic protection as combinational or mono-therapy.

1. Introduction

Over 2000 years ago, diabetes mellitus (DM) firstly appeared in medicinal text (Orhan et al., 2012). DM is a very common health problem, the incidence of this disease rapidly increases day by day, worldwide (Arunachalam and Parimelazhagan, 2013). DM is a chronic disorder of derangement of carbohydrate, protein and fat metabolism distinguished by enhanced blood glucose level and causes a defect in the action of insulin, insulin secretions or both conditions (Irudayaraj et al., 2012). During hyperglycemia starts the production of non enzymatic glycation of protein and reactive oxygen species (ROS), which plays an important role in the development of DM complications (Dewanjee et al., 2009). Oxidative stress plays an important role in the development of diabetes pathology and an essential trigger in complex series of events, which starts the enhancement of the occurrence of atherosclerosis. Antioxidants play an important role in the tissue protection from ROS and oxidative stress. Antioxidant also enhances the immune system and decline the risk factor of diabetes (Deore et al., 2011). A lot of natural sources based drug are worldwide Known as hypoglycemia (Ahmed et al., 2014, 2015), antioxidant or both activities (Kumar et al., 2014). A lot of synthetic drugs viz., biguanide, sulfonylureas, α-glycosidase inhibitors, meglitinides, thiazolidinedione, dipeptidyl peptidase-4 inhibitors and insulin are available in market, but no one drug gives the long duration of action to controlling the blood glucose level without causing any adverse side effects (Lee et al., 2012; Singh et al., 2007; Xing et al., 2009). Due to a short action of synthetic drug along with adverse side effects, there is growing interest in using plant based drugs, remedies, or isolated compounds in the treatment of diabetes (Sunil et al., 2012). Plant derived drugs and their products have attracted not only curing the diseases and health problems, but also take part in the development of new drugs discovery. The plant derived drug discovery developments are still major focusing on the development of therapeutics for various types of diseases including diabetes. Although the availability of known antihyperglycemic medicine on the pharmaceutical market, researcher still searching the new source of plant based drug with effectual action with fewer side effects in diabetes mellitus complications (Badole and Bodhankar, 2010). The World Health Organization (WHO) expert committee has recommended that more studies on plant based drugs and their isolated compounds for the treatment of DM (World Health Organization, 1980). According to WHO, plant based drugs are very effective in the management of diabetes with less or no side effects and are very low cost effective drugs. Metformin (*Galega officinalis*) is an approved herb used as an antidiabetic drug which is obtained from plant source (Marles and Farnsworth, 1995). This viewpoint outlines the opportunity that exists for these herbs in the management of diabetes and the state of the evidence for their clinical antidiabetic efficacy (Vuksan and Sievenpiper, 2005).

Nowadays, a lot of researchers and scientists are working on natural plant based drugs as validation of the immense potential of traditional medicinal plants in whole over world (Gupta et al., 2010). Ethanobotanical history showed that the more than 800 plants are used as traditional remedies in the treatment of diabetes mellitus.

Garcinia mangostana L. (Clusiaceae), commonly known as mangosteen, is a slow-growing tropical evergreen tree with glabrous and leathery leaves. The height of plant is 6–25 m and is commonly found in India, Myanmar, Sri Lanka, and Thailand. The color of fruit *Garcinia mangostana* L. and is red-purple to dark purple in color. The edible aerial part of fruit is white, juicy, spongy, and slightly acidic in taste with pleasant aroma (Martin, 1980). The pericarp of mangosteen has been used in Thai indigenous medicine for the treatment of skin infections, wounds, and diarrhea for many years (Gupta et al., 2010; Martin, 1980). Recently, products manufactured from *G. mangostana* have been used as a botanical dietary supplement mainly in United States, due to potent antioxidant activity (Mahabusarakam et al., 1987). The major secondary metabolites of mangosteen have been found to be prenylated xanthone derivatives (Moongkarndi et al., 2004; Nguyen et al., 2005; Suksamrarn et al., 2002, 2003). Some members of this compound class isolated from this plant possess antifungal (Gopalakrishnan et al., 1997), antimicrobial (Suksamrarn et al., 2002), antioxidant (Yoshikawa et al., 1994) and cytotoxic activities (Ho et al., 2002). Antioxidants play an important role in inhibiting and scavenging free radicals, thus providing protection against infection and degenerative diseases viz., diabetes, cancer, virus, etc.

From this viewpoint, the present study was carried out to evaluate the potential effect of α-mangostin mediated pharmacological modulation of hepatic carbohydrate metabolism in diabetic rats.

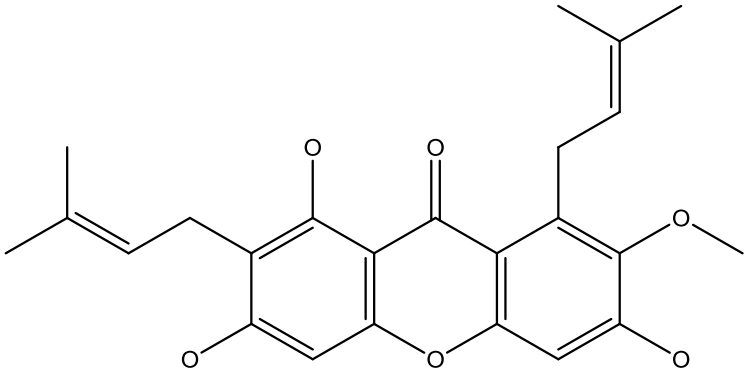
2. Material and methods

2.1. *Drugs/chemicals*

α-Mangostin (Fig. 1a) was a kind gift received from AIMIL Pharmaceuticals, New Delhi. Streptozotocin (Sigma Chemical Co. USA), GOD/POD kit, Cholesterol kit, Triglyceride kit, (Span, India), Glibenclamide (Ranbaxy, India), Carboxyl methyl cellulose (CMC) (SD fine, India) were purchased from respective vendors. The entire reagent utilized for experimental protocol was of analytical grade and used without further purification.

2.2. *Molecular docking studies*

The molecular docking study was carried out on 3D structure of 11-β-hydroxysteroid dehydrogenase complex enzyme using Maestro 9.0 program (Schrodinger Inc. USA) with 64 bits operating systems under Windows 7 with an HCl computer [Intel (R) Core (TM) i5-2400 CPU @ 3.10 GHz, 8 GB memory]. The enzyme used in the study was taken from Protein Data Bank (PDB ID: 2BEL) which has 96% similarity with the human cell enzyme and all active site residues in the vicinity of cofactor have exact counterparts and the structure was refined as follows. The enzyme structure was checked for missing atoms, bonds and contacts. Water molecules and all residues other than ligand were manually deleted. The ligand molecule was constructed using the builder molecule and were energy



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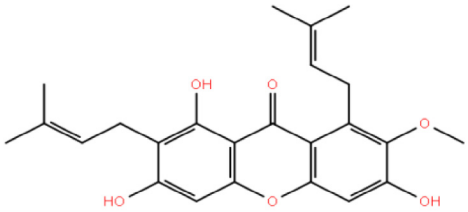

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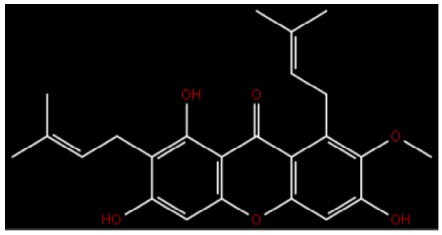

c

Fig. 1 – a: **Structure of α-mangostin,** b,c: **Ligand 3D structure.**

minimized. The active site was generated using the grid box. The lowest energy conformation was selected and subjected to an energy minimization.

2.3. Animals

Swiss albino (Wistar strain) rats (sex, male), 175 to 200 g body weight, were kept in individual polyethylene cages and housed in an air conditioned room at 20 ± 2 °C; 40–60% humidity with 12 h light and 12 h dark circle; at the animal house facility of Siddhartha Institute of Pharmacy, Dehradun, Uttarakhand, India, in accordance with Animal Ethical Committee of Siddhartha Institute of Pharmacy and Institutional Animal Ethics Committee (IAEC) recognized by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, for care and use of laboratory animals.

2.4. Acute oral toxicity study

The oral study of α-mangostin was tested for short term and acute toxicity on Wistar rats. During the acute toxicity study, all rats were randomly divided into different groups and each group contain 6 animals; all grouped animals received the graded doses of α-mangostin (0.01, 0.05, 0.25, and 1.25 g kg^{-1}) and were observed for following parameters viz., neurological, behavioral and autonomic changes for 48 hours (Kumar et al., 2013a, 2013b, 2013c).

To estimate short term toxicity, rats were randomly divided into 5 groups (6 animals; 3 male and 3 female) and each group received the graded doses (single dose daily per oral) of α-mangostin for 28 days. All animals were monitored for any toxicity, clinical symptoms and adverse reactions. Body weight, water and food consumption were monitored at regular interval. Blood was collected from all animals into the heparinzed tubes, for estimation of the hematological and biochemical parameters.

2.5. Effect of α-mangostin on glucose-loaded model (oral glucose tolerance test)

Oral glucose tolerance test (OGTT) test was performed on overnight (12 h) starving Wistar rats. The rats were randomly divided into seven groups and each group contains 6 rats (Kumar et al., 2013a, 2013b, 2013c). Group I: rats were treated with vehicle only, Group II: rats were treated with α-mangostin 100 mg/kg, body weight, Group III: rats were treated with glucose 2 g/kg, body weight, Group IV: rats were treated with α-mangostin 25 mg/kg, body weight, Group V: rats were treated with α-mangostin 50 mg/kg, body weight, Group VI: rats were treated with α-mangostin 100 mg/kg, body weight, and Group VII: rats treated with Glibenclamide 10 mg/kg, body weight. All group rats received the per-determined doses after receiving the 2 mg/kg of glucose except for normal control group rats who were treated with α-mangostin (100 mg/kg). To determine blood glucose level, blood was collected from the tail vein at regular intervals (0, 30, 60, 90, 120, and 150 min). The blood glucose level of all groups rat was determined by GOD-POD kit following the given instruction by manufacturer.

2.6. Induction of diabetes

Swiss albino (Wistar strain) rats were used for experimental study. Before the experimentation all rats were starving overnight (12 h). Single intraperitoneal injection of STZ (streptozotocin) (60 mg/kg, body weight) prepared by STZ dissolving in 0.1 M citrate buffer (pH = 4. 5). Rats of normal control and normal control group treated with α-mangostin (100 mg/kg) received equal volume of vehicle. After 7 days, diabetes was confirmed by elevating the blood glucose level and the rats having blood glucose level more than 250 mg/dl used for study (Ahmed et al., 2013).

2.7. Experimental study design

Diabetic rats randomly divided into following groups. Group I: rats were treated with vehicle only; Group II: rats were treated with α-mangostin 100 mg/kg, body weight; Group III: rats were treated with STZ only, body weight; Group IV: rats received STZ + α-mangostin 25 mg/kg, body weight; Group V: rats received STZ + α-mangostin 50 mg/kg, body weight; Group VI: rats received STZ + α-mangostin 100 mg/kg, body weight; Group VII: rats received STZ + Glibenclamide 10 mg/kg, body weight. All group rats received the oral administration of different doses of α-mangostin and glibenclamide through the intragastric tube for 56 days.

2.7.1. Biochemical estimation

All group rats were starved overnight and blood sample was withdrawn from tail vein. The blood was withdrawn from the all groups of rats at regular time intervals (1st 28th and 56th day). Plasma insulin level and blood glucose level were determined by using the reported method of Zheng et al., 2012 with minor modification (Zheng et al., 2012). The body weight of all group rats was estimated at regular intervals. End of experimental study (56th day), all group animals were fasted overnight and blood samples were collected from tail vein for the estimation of biological parameters viz., hexokinase, glucose-6-phosphatase, fructose-16-bisphosphatase; lipid parameters viz., total cholesterol (TC), total triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and very low density lipoprotein (VLDL) (Kumar et al., 2013a, 2013b, 2013c). The coronary risk index and atherogenic index were calculated using the described formula

$$\text{Atherogenic Index} = \frac{\text{Low density lipoprotein cholesteol (LDL)}}{\text{High density lipoprotein cholesterol (HDL)}}$$

$$\text{Coronary Risk Index} = \frac{\text{Total Cholesterol (TC)}}{\text{High density lipoprotein cholesterol (HDL)}}.$$

The ponderal homogeneity index (iPH) and ponderal grain (PG) were calculated by using the following formula.

$$iPH = 2\,Wi\frac{Wi}{(Wi + Wh)}$$

$$PG = \frac{(Wf - Wi)}{Wf} \times 100$$

Where Wi = initial body weight; Wh = highest body weight; Wf = final body weight.

2.7.2. *Estimation of antioxidant markers*

The antioxidant marker parameters including lipid peroxidation (LPO) in tissue was evaluated by using the reported method of Ohkawa et al., 1979 with minor modification (Ohkawa et al., 1979), superoxide dismutase (SOD) and catalase (CAT), reduced glutathione (GSH) were estimated by reported method EI-Beshbishy (2005; Anwar et al., 2015; Kumar et al., 2015a, 2015b; Verma et al., 2016).

2.7.3. *Estimation of renal parameters*

Renal parameters such as creatinine (CRE), total blood urea nitrogen (BUN) and glycated serum protein (GSP) were evaluated by using the diagnostic kit according to manufacturer's instruction.

2.7.4. *Estimation of serum CRP, TNF-α and IL-6*

The level of CRP, TNF-α and IL-6 were estimated by according to the manufacture's instruction using the ELISA method.

2.8. *Data analyses*

Statistical analyses were executed by Graphpad prism software. Results were presented as mean value ± standard deviation. The Dunnett's test was performed for analysis the data, respectively.

3. Result

3.1. *Molecular docking study*

Docking of α-mangostin with 11-hydroxysteroid dehydrogenase (PDB ID: 2BEL) active site revealed several molecular interactions (hydrogen bond and hydrophobic interactions) were considered to be responsible for the observed affinity of compound. In contrast, α-mangostin lacks of Zwitter ion but its form hydrogen bonds to enzyme through its amino and carbonyl group with SER169 residue, that is at the same residue where the natural inhibitors bind. Hydrogen bond interaction between active hydrogen (—H—O—) of α-mangostin, as it acts as a hydrogen bond donor with the carboxyl group (C═O) of side chain residue of SER169 (1.90 Å) as it act as hydrogen bond acceptor. Further, second Hydrogen bond interaction with ring oxygen g (—O—) of compound as it acts as the hydrogen bond acceptor and an amino group (N—H) of side chain residue of SER170 (2.10 Å) as it acts as hydrogen bond donor (Figs. 2 and 3). The hydroxyl compound group seems to have an important role in strong hydrogen bonding because the lone pair of electrons of nitrogen atoms of amide delocalized into carbonyl group of compounds. In addition to many hydrophobic interactions between phenyl ring and a side group with rest amino acid residues were shown in Lig plot (Fig. 3). The glide score value of the compound was found to be –7.94 as it indicated that the molecule interacts better with the enzyme.

Docking of compound into the enzyme Fructose-1, 6-bisphosphatase 1 (PDB ID: 2JJK) active site revealed that several molecular interactions (hydrogen bond and hydrophobic

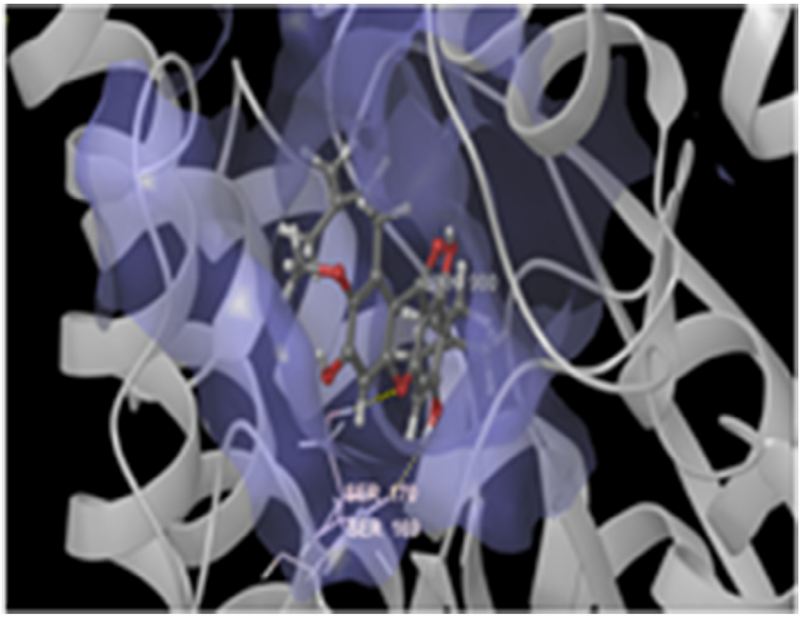

Fig. 2 – Binding patterns of compound α-mangostin into the binding sites of 11-β-hydroxysteroid dehydrogenase (PDB ID: 2BEL) showing hydrogen bond (yellow dotted lines) with SER169 (1.90 Å) and with SER170 (2.10 Å).

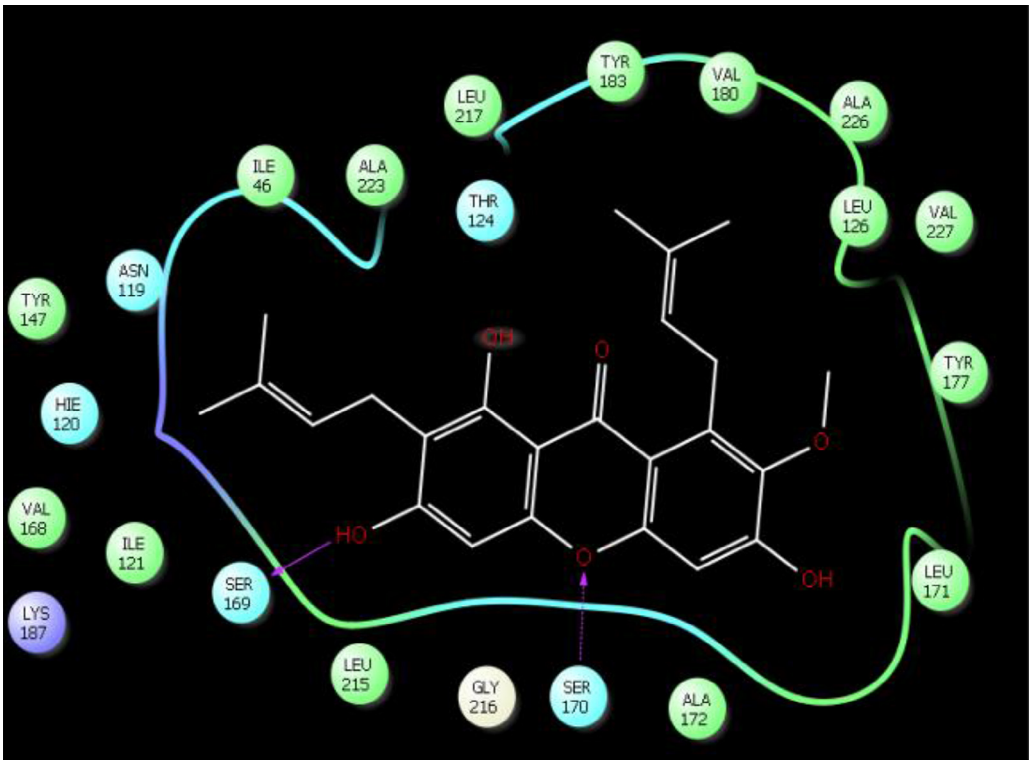

Fig. 3 – Lig plot of compound α-mongestin displays interaction with the binding sites of 11-β-hydroxysteroid dehydrogenase enzyme (PDB ID: 2BEL) showing hydrogen bond (pink dotted lines) with SER169 (1.90 Å) and with SER170 (2.10 Å).

interactions) were considered to be responsible for observed affinity of compound. In contrast, compound lacks Zwitter ion but its form hydrogen bonds to the enzyme through its amino and carbonyl group with SER169 residue that is at the same residue where the natural inhibitors bind. Hydrogen bond interaction between the active hydrogen (—H—O—) of compound as it acts as a hydrogen bond donor with the carboxyl group (C═O) of side chain residue of ARG C:22 (2.4938 Å) as it act as hydrogen bond acceptor. Further second Hydrogen bond interaction with ring oxygen g (—O—) of the compound as it acts as the hydrogen bond acceptor and an amino group (N—H) of the side chain residue of GLY A:26 (2.002 Å) as it acts as hydrogen bond donor (Figs. 4 and 5). The hydroxyl group of the compound seems to have an important role in strong hydrogen bonding because the lone pair electrons of nitrogen atom of the amide delocalized into the carbonyl group of compounds. In addition to many hydrophobic interactions between the phenyl ring and a side group with the rest amino acid residues were shown in Lig plot (Fig. 5). The glide score value of the compound was found to be –6.449 as it indicated that the molecule interacts better with the enzyme.

Docking study of the glibenclamide (Fig. 6) into the enzyme 11-hydroxysteroid dehydrogenase (PDB ID: 2BEL) active site showed the several molecular interactions (hydrogen bond and hydrophobic interactions) were considered to be responsible for the observed affinity of the glibenclamide. In contrast, glibenclamide lacks Zwitter ion but it forms hydrogen bonds with the enzyme through its amino and carbonyl groups with the LEU 215 residue that is at the same residue where the natural inhibitors bind. Hydrogen bond interaction between the active hydrogen (—H—O—) of the compound as it acts as a hydrogen bond donor with the carboxyl group (C═O) of the side chain residue of LEU 215 (1.71 Å) as it acts as hydrogen bond acceptor. Further second Hydrogen bond interaction with ring oxygen g (—O—) of the compound as it acts as the hydrogen bond acceptor and an amino group (N—H) of the side chain residue of SER170 (2.15 Å) as it acts as hydrogen bond donor (Figs. 7 and 8). The hydroxyl group of the compound seems to have an important role in strong hydrogen bonding because the lone pair of electrons of nitrogen atoms of the amide delocalized into the carbonyl group of compounds. In addition to many hydrophobic interactions between the phenyl ring and a side group with the rest of the amino acid residues were shown in Lig plot (Fig. 8). The glide score value of the compound was found to be –7.33 as it indicated that the molecule interacts better with the enzyme.

Docking study of the glibenclamide into the enzyme Fructose-1, 6-bisphosphatase 1 (PDB ID: 2JJK) active site showed that several molecular interactions (hydrogen bond and hydrophobic interactions) were considered to be responsible for the observed affinity of the glibenclamide. (——) — Further, second Hydrogen bond interaction with ring oxygen g (-O-) of the compound acts as the hydrogen bond acceptor and an amino group (N-H) of the side chain residue of THR A: 31 (2.39 Å) act as hydrogen bond donor (Figs. 9 and 10). The hydroxyl group of the compound seems to have an important role in strong hydrogen bonding because the lone pair of electrons of nitrogen atoms of the amide delocalized into

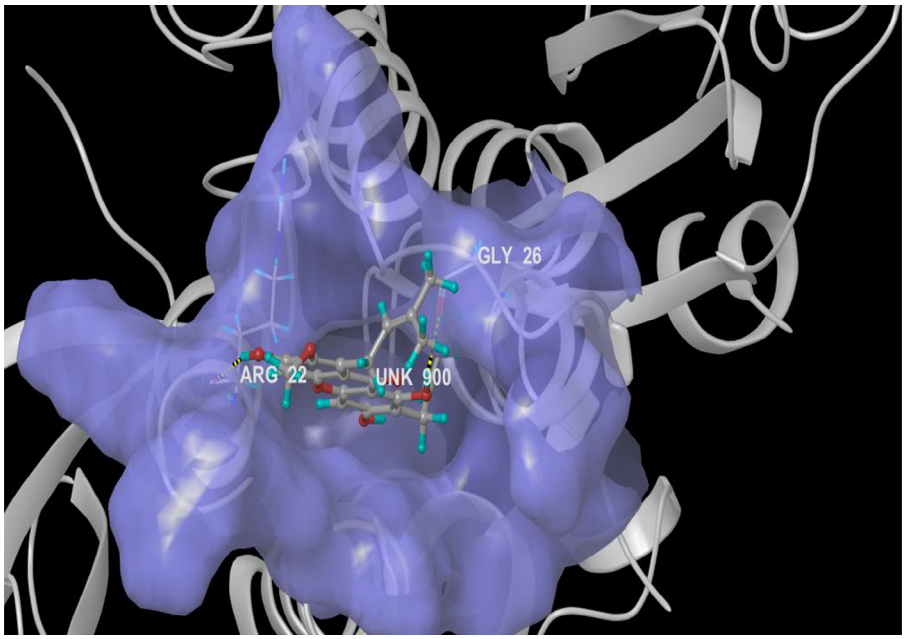

Fig. 4 – Binding patterns of compound α-mongestin into the binding sites of fructose-1, 6-bisphosphatase 1 (PDB ID: 2JJK) showing hydrogen bond (yellow dotted lines) with ARG 22 (2.49 Å) and with GLY 26 (2.00 Å).

the carbonyl group of compounds. In addition to many hydrophobic interactions between the phenyl ring and a side group with the rest of the amino acid residues were shown in Lig plot (Fig. 10). The glide score value of the compound was found to be –7.36 as it indicated that the molecule interacts better with the enzyme.

3.2. *Acute oral toxicity*

Oral administration of α-mangostin did not show any sign and symptoms of toxicity, mortality, behavioral changes and none of any other types of adverse reaction during the study period. During the specified study period, no difference was

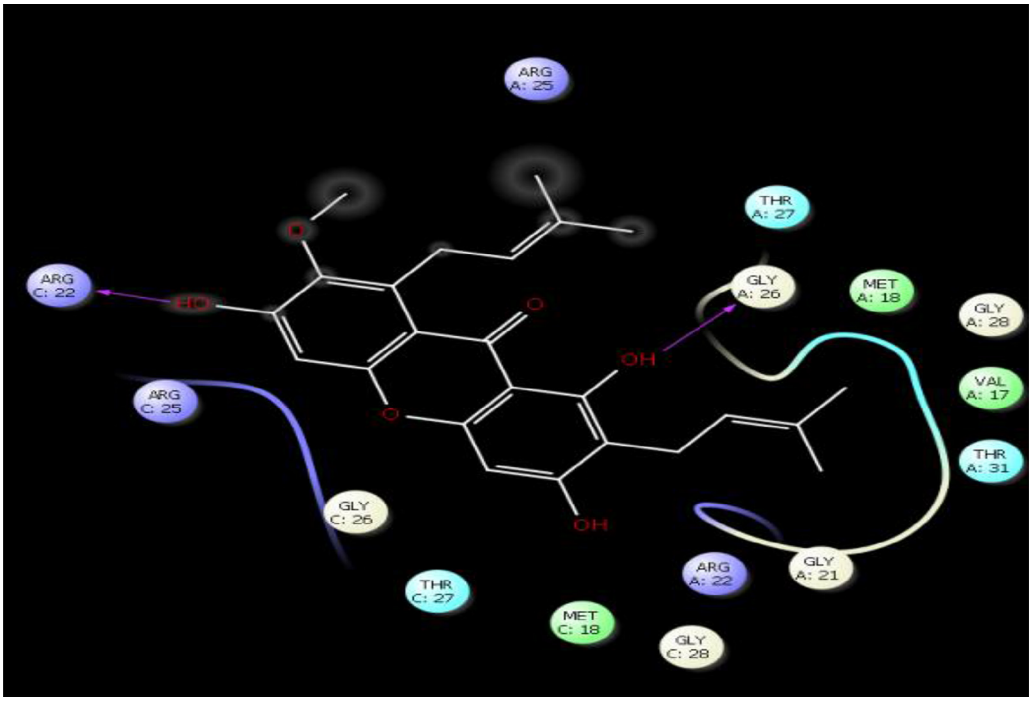

Fig. 5 – Lig plot of compound α-mongestin display interaction into the binding sites of fructose-1,6-bisphosphatase 1 (PDB ID: 2JJK) showing hydrogen bond (pink dotted lines) with ARG 22 (2.49 Å) and with GLY 26 (2.00 Å).

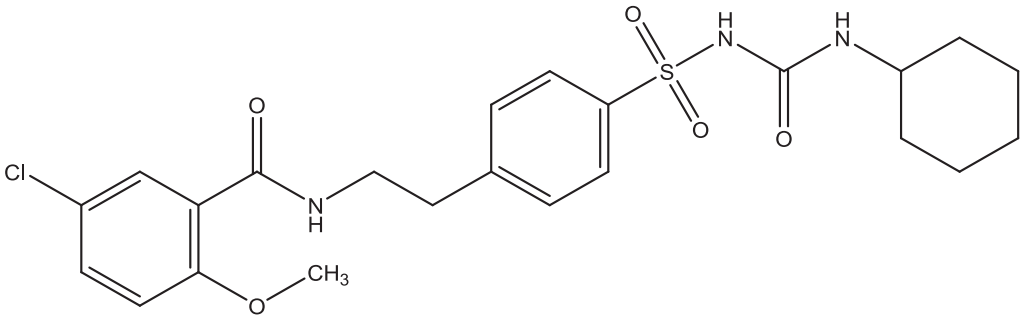

Fig. 6 – Structure of Glibenclamide.

observed in body weight and food consumption when compared to normal control group rats. Other parameters viz., hepatic, renal and hematological profile remained unchanged after 28 days of utilization (Table 1). Oral administration of α-mangostin did not produce any toxic effect in rats till the dose 1250 mg/kg body weight therefore, further experimentation of antidiabetic activity of α-mangostin was carried out using 25, 50 and 100 mg/kg dose levels.

3.3. *Effect of α-mangostin on blood glucose tolerance test*

The acute effect of α-mangostin on blood glucose level was evaluated using an oral glucose tolerance test on overnight fasted rats. After receiving glucose; glucose control group rats showed the increased area under control (AUC) of blood glucose (Table 2). While α-mangostin received rats showed the declined level of blood glucose AUC at dose dependent manner (Fig. 3). Oral administration of α-mangostin significantly ($P < 0.001$) reduced the blood glucose level by 13.58%, 24.07% and 37.45% at the tested doses of 25 mg/kg, 50 mg/kg and 100 mg/kg respectively, after glucose administration in rats.

3.4. *Effect of α-mangostin on blood glucose*

The blood glucose level of normal control and experimental rats was estimated at regular intervals. Normal control and normal control group rats treated with α-mangostin (100 mg/kg) did not show any change in blood glucose level till end of experimental periods. STZ induced diabetic rats showed the enhanced blood glucose level at end of the study. STZ induced diabetic rats treated with α-mangostin (25, 50 and 100 mg/kg) had significantly ($P < 0.001$) declined blood glucose level at effective dependent manner. α-Mangostin dose of 100 mg/kg, b.w. showed the maximum declined blood glucose at end of the study. STZ induced diabetic rats treated with glibenclamide (standard drug) showed the declined level of blood glucose (Table 3).

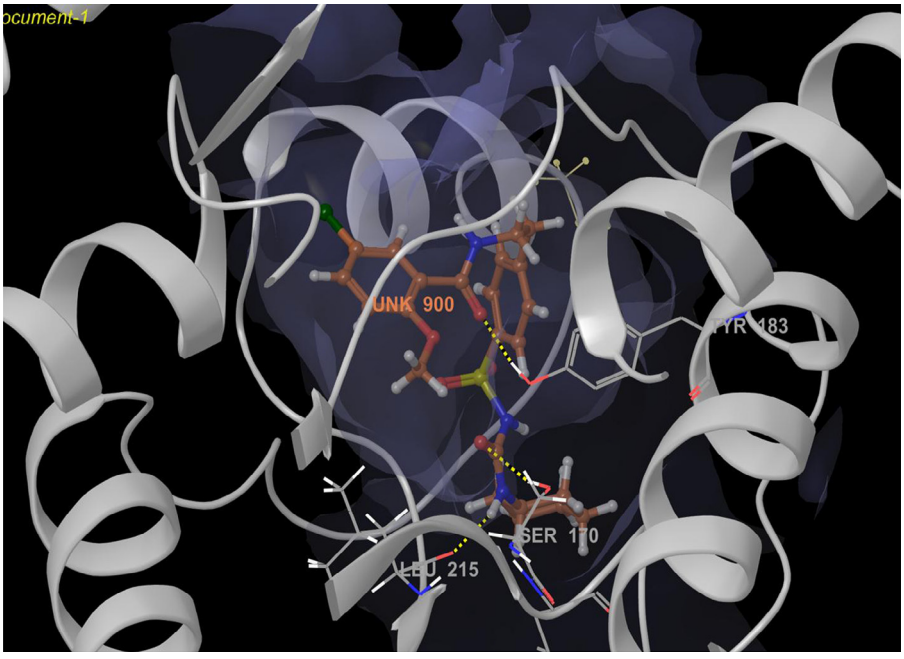

Fig. 7 – Binding patterns of Glibenclamide into the binding sites of 11-β-hydroxysteroid dehydrogenase (PDB ID: 2BEL) showing hydrogen bond (yellow dotted lines) with LEU 215 (1.71 Å), SER170 (2.15 Å) and with TYR 183 (2.43 Å).

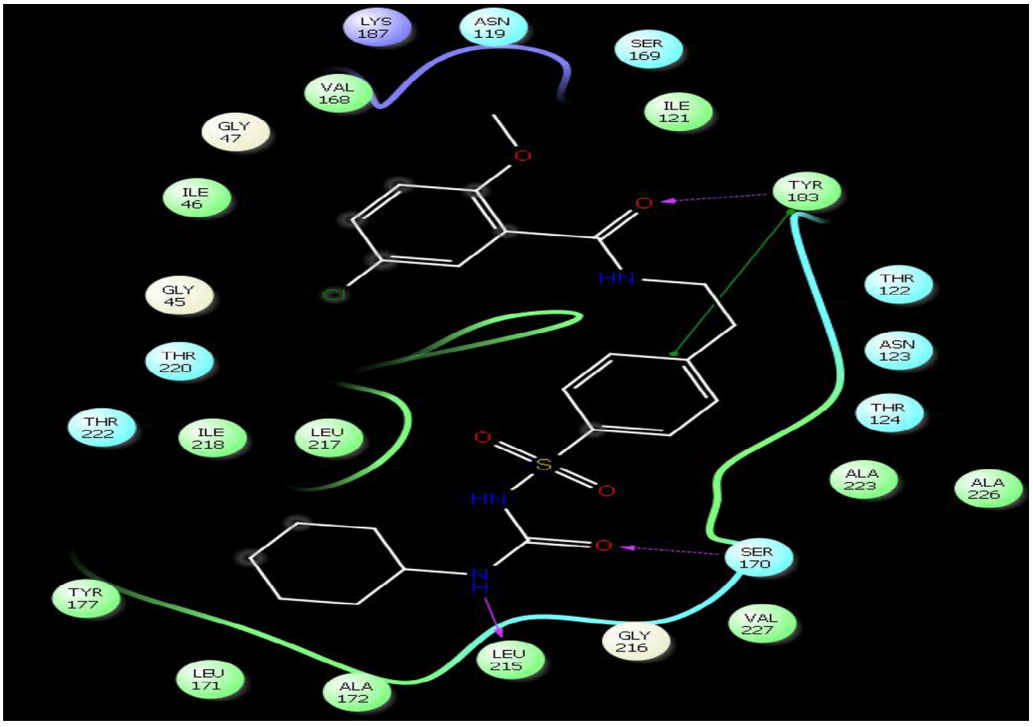

Fig. 8 – Lig plot of Glibenclamide display interaction into the binding sites of 11-β-hydroxysteroid dehydrogenase enzyme (PDB ID: 2BEL) showing hydrogen bond (pink dotted lines) with LEU 215 (1.71 Å), SER170 (2.15 Å) and with TYR 183 (2.43 Å) and, Pi–Pi interaction with TYR 183 (4.59 Å).

3.5. *Effect of α-mangostin on weight variation*

The PG and iPH for normal control and experimental diabetic rats were calculated and summarized in Table 4. End of the study, STZ induced diabetic rats demonstrated the declined body weight as compared to normal control group rats. STZ induced diabetic rats treated with α-mangostin (25, 50 and 100 mg/kg) and glibenclamide significantly ($P < 0.001$) enhanced the body weight at dose dependent manner. α-Mangostin 25 mg/kg produced 196 g (3.78%), 50 mg/kg 206.8 g (6.74%) and 100 mg/kg 209 g (11.49%)

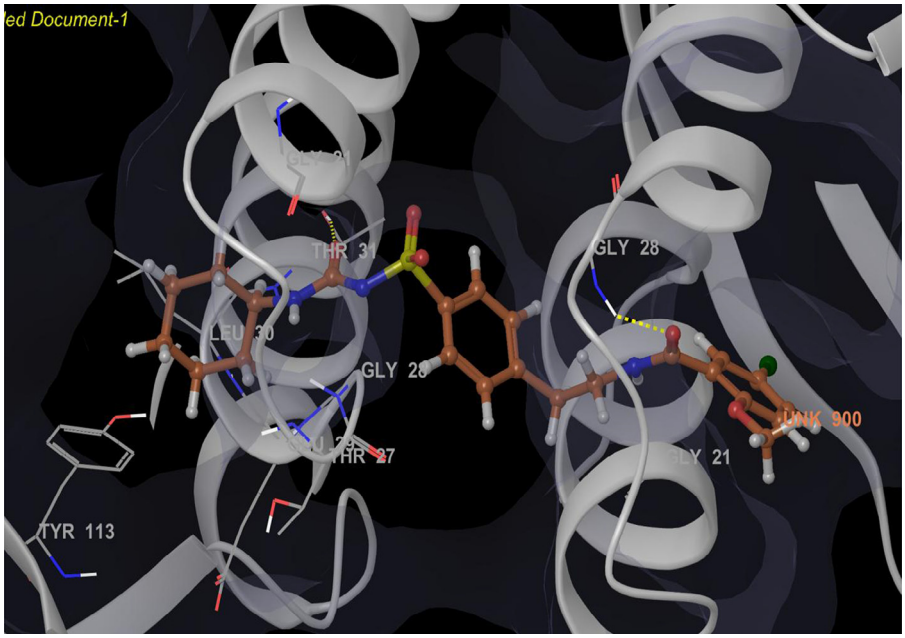

Fig. 9 – Binding patterns of Glibenclamide into the binding sites of fructose-1, 6-bisphosphatase 1 (PDB ID: 2JJK) showing hydrogen bond (yellow dotted lines) with THR A: 31 (2.39 Å) and with GLY C: 28 (1.98 Å).

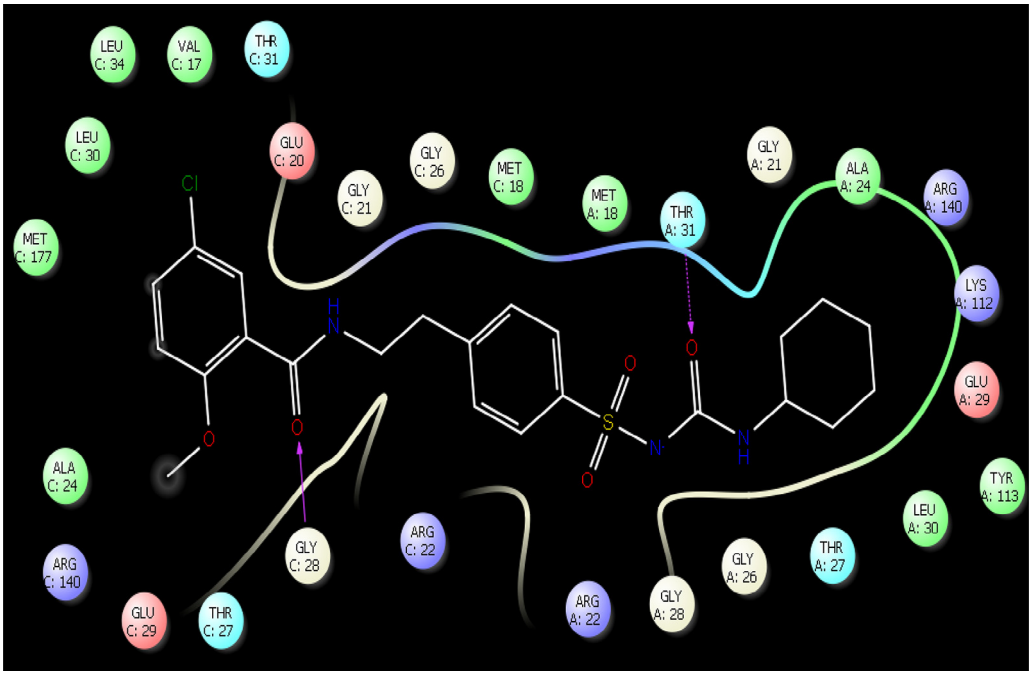

Fig. 10 – Lig plot of Glibenclamide display interaction into the binding sites of fructose-1,6-bisphosphatase 1 (PDB ID: 2JJK) showing hydrogen bond (pink dotted lines) with THR A: 31 (2.39 Å) and with GLY C: 28 (1.98 Å).

Table 1 – Effect of 28 day repeated oral administration of α-mangostin on biochemical and hematological parameters of rats.

S. No	Sex	Parameter	Toxicity study				
			Normal control	α-Mangostin (10 mg /kg)	α-Mangostin (50 mg/kg)	α-Nangostin (250 mg/kg)	α-Mangostin (1250 mg/kg)
General effect							
1	Male	Body weight (g)	172 ± 4.34	168.4 ± 2.21	176 ± 4.32	181.43 ± 3.84	192 ± 3.54
2	Male	Water intake (mL)	108	102	105	110	115
3	Male	Food intake (gm)	65	64	68	71	74
1	Female	Body weight (gm)	123 ± 2.84	118 ± 1.82	122 ± 2.54	129 ± 3.84	131 ± 1.32
2	Female	Water intake (mL)	78	70	76	80	84
3	Female	Food intake (gm)	40	38	41	42	41
Hematological parameters							
1	Male	RBC (10^6/cu mm)	6.46 ± 0.98	7.21 ± 1.07	6.65 ± 1.45	8.41 ± 1.94	8.32 ± 1.63
2	Male	WBC (10^3/cu mm^3)	9.87 ± 1.11	10.73 ± 1.84	11.21. ± 1.82	9.92 ± 1.21	9.96 ± 1.93
3	Male	Hb (g dL^{-1})	14.21 ± 1.92	13.41 ± .98	13.98 ± 1.09	14.31 ± 1.92	14.11 ± 0.92
4	Male	Platelet (10^5/cu mm)	4.32 ± 0.42	5.8 ± 0.93	6.7 ± 1.03	4.78 ± 0.93	4.57 ± 0.73
1	Female	RBC (10^6/cu mm)	5.94 ± 0.87	5.64 ± 1.21	5.87 ± 1.92	6.11 ± 0.93	6.16 ± 0.98
2	Female	WBC (10^3/cu mm^3)	8.65 ± 1.09	9.92 ± 1.14	10.8 ± 1.08	9.01 ± 1.22	8.87 ± 1.74
3	Female	Hb (g dL^{-1})	15.32 ± 1.93	16.67 ± 1.83	16.21 ± 2.93	15.94 ± 1.98	15.45 ± 1.73
4	Female	Platelet (10^5/cu mm)	4.01 ± 0.31	3.98 ± 1.83	4.2 ± 0.97	4.6 ± 1.04	5.04 ± 0.82
Biochemical parameters							
1	Male	Bilirubin (mg dL^{-1})	0.48 ± 0.07	0.51 ± 0.04	0.54 ± 0.09	0.52 ± 0.07	0.50 ± 0.06
2	Male	Creatinine (mg dL^{-1})	0.76 ± 0.21	0.86 ± 0.63	0.91 ± 0.84	0.88 ± 0.92	0.79 ± 1.01
3	Male	Urea (mg dL^{-1})	41 ± 3.43	36.2 ± 2.34	40.83 ± 2.91	43.8 ± 4.53	42.6 ± 2.32
4	Male	ALP (UL^{-1})	288.2 ± 31.5	301 ± 40.3	321.6 ± 32.5	358 ± 39.8	313.5 ± 29.4
5	Male	ALT (UL^{-1})	75.9 ± 4.32	61.5 ± 5.31	66.9 ± 3.41	70.42 ± 4.52	72.4 ± 2.76
6	Male	AST (UL^{-1})	121.4 ± 10.4	124.6 ± 10.8	132 ± 9.82	124 ± 12.43	113 ± 8.92
1	Female	Bilirubin (mg dL^{-1})	0.43 ± 0.04	0.41 ± 0.08	0.39 ± 0.06	0.44 ± 0.03	0.45 ± 0.08
2	Female	Creatinine (mg dL^{-1})	0.65 ± 0.98	0.61 ± 1.24	0.64 ± 1.73	0.69 ± 1.92	0.72 ± 1.62
3	Female	Urea (mg dL^{-1})	35 ± 2.23	35.1 ± 4.32	33 ± 3.94	36.4 ± 1.94	38.8 ± 2.08
4	Female	ALP (UL^{-1})	250.2 ± 22.9	275.9 ± 32.8	279 ± 26.98	301.92 ± 30.21	312 ± 28.72
5	Female	ALT (UL^{-1})	65.55 ± 2.32	64.53 ± 3.44	60.3 ± 2.83	62.93 ± 4.93	59.3 ± 2.93
6	Female	AST (UL^{-1})	99.8 ± 11.22	111.2 ± 14.32	118 ± 10.92	107.2 ± 9.02	98.4 ± 10.23

Table 2 – Pharmacokinetic parameters effect of α-mangostin on blood glucose levels in oral glucose tolerance test in normoglycemic rats.

S. No	Groups	Pharmacokinetic parameters		
		C_{max} (mg/dl)	t_{max} (min)	AUC (mg.min/dl)
1	Glucose control	144.8 ± 2.341	30	17794.5
2	α-Mangostin (25 mg/kg)	139.2 ± 1.497	30	16779
3	α-Mangostin (50 mg/kg)	135.8 ± 2.321	30	15937.5
4	α-Mangostin (100 mg/kg)	125.3 ± 1.356	30	13878
5	Glibenclamide (10 mg/kg)	128.3 ± 1.548	30	14496

Each parameter represents the mean of Six animals. Area under curve (AUC) values. tmax, time at maximum observed concentration; Cmax, maximum concentration.

confirm the increased body weight respectively, when compared to STZ induced diabetic control group rats 175 g (–2.85%).

3.6. *Effect of α-mangostin on insulin, HOMA-IR, HOMA-β hemoglobin and glycated hemoglobin*

Table 5 clearly depicted the effect of α-mangostin on insulin, hemoglobin and glycated hemoglobin in normal control and experimental animals. STZ induced diabetic rats showed the increased level of glycated hemoglobin and decreased plasma insulin and hemoglobin levels. Oral administration of α-mangostin significantly ($P < 0.001$) enhanced the level of insulin, hemoglobin and declined the level of glycated hemoglobin. STZ induced diabetic rats treated with α-mangostin showed the protective effect against insulin resistance at effective dose dependent manner.

Table 3 – Effect of α-mangostin on blood glucose level in normal & STZ induced diabetic treated rats.

S. No	Groups	Blood glucose level in mg/dL at different time interval of experimentation		
		On 1st day	On 28th day	On 56th day
1	Normal control	79.8 ± 1.023	83.5 ± 0.934	84.1 ± 1.254
2	Normal control + α-mangostin (100 mg/kg)	80.6 ± 1.208	81.2 ± 1.034	83.5 ± 1.039
3	Diabetic control	322.4 ± 2.768	403.3 ± 2.039	481.6 ± 2.383
4	α-Mangostin (25 mg/kg)	320.6 ± 1.923^{ns}	225.2 ± 1.093***	190.4 ± 1.839***
5	α-Mangostin (50 mg/kg)	320 ± 1.871^{ns}	202.5 ± 1.536***	134.2 ± 1.092***
6	α-Mangostin (100 mg/kg)	324.2 ± 1.563^{ns}	183.4 ± 1.021***	96.8 ± 1.732***
7	Glibenclamide (10 mg/kg)	327.5 ± 2.514^{ns}	188.3 ± 1.032***	101.6 ± 0.928***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin.
*$p < 0.05$ is considered as very significant when compared to the control group.
**$p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 4 – Effect of α-mangostin on body weight and ponderal homogeneity index (iPH) and ponderal gain (PG) of STZ induced diabetic and normal control rats.

S. No	Groups	Initial weight (g)	Final weight (g)	iPH	PG
1	Normal control	178.8 ± 1.462	198.4 ± 1.544	0.948	9.879
2	Normal control + α-mangostin (100 mg/kg)	185.2 ± 1.885	205.8 ± 1.748	0.947	10.001
3	Diabetic control	180 ± 1.951	180.2 ± 2.286	1.014	0.111
4	α-Mangostin (25 mg/kg)	188.6 ± 1.784	196 ± 1.249**	0.981	3.775
5	α-Mangostin (50 mg/kg)	193 ± 3.036	206.8 ± 3.467***	0.965	6.673
6	α-Mangostin (100 mg/kg)	185 ± 1.428	209 ± 1.108***	0.939	11.483
7	Glibenclamide (10 mg/kg)	198.4 ± 1.841	220 ± 1.239***	0.948	9.818

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin.
*$p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 5 – Effect of α-mangostin on biochemical parameters in STZ-induced diabetic rats.

S. No	Groups	Biochemical parameters				
		Plasma insulin (μU/mL)	Glycated hemoglobin (A1c) (%)	Hemoglobin (cells/cu.mm)	HOMA-IR	HOMA-β
1	Normal control	12.8 ± 0.378	5.4 ± 0.493	13.2 ± 0.374	2.80	218.38
2	Normal control + α-mangostin (100 mg/kg)	12.6 ± 0.245	5.2 ± 0.379	13.6 ± 0.245	2.59	221.26
3	Diabetic control	3.2 ± 0.393	9 ± 0.705	6.8 ± 0.374	3.81	2.75
4	α-Mangostin (25 mg/kg)	4.8 ± 0.254*	8.2 ± 0.374^{ns}	8 ± 0.832**	2.25 ^{ns}	13.56*
5	α-Mangostin (50 mg/kg)	7.2 ± 0.832**	6.8 ± 0.272*	10 ± 0.793***	2.38*	36.40**
6	α-Mangostin (100 mg/kg)	12 ± 0.634***	5.2 ± 0.194***	12.8 ± 0.375***	2.86**	127.81***
7	Glibenclamide (10 mg/kg)	11.6 ± 0.509***	5.8 ± 0.394***	12.4 ± 0.593***	2.91**	108.18***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin.
* $p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

3.7. *Effect of α-mangostin on hepatic enzymes*

Table 6 represented the efficacy of α-mangostin on hepatic enzymes viz., hexokinase, glucose-6-phosphatase and fructose 1–6 biphosphate in STZ induced diabetic rats. Increased levels of glucose-6-phosphatase, fructose 1–6 phosphatase and decreased level of hexokinase, glucose-6-phosphate dehydrogensae was observed in STZ induced diabetic rats. STZ induced diabetic rats treated with α-mangostin (25, 50 and 100 mg/kg) and glibenclamide significantly ($P < 0.001$) declined the level of glucose-6-phosphatase, fructose-6-phosphatase and increased level of hexokinase at effective dose dependent manner.

3.8. *Effect of α-mangostin on lipid profile*

Table 7 clearly illustrated the effect of α-mangosteen on lipid profile of STZ induced diabetic rats. Table 7 showed the increased level of total cholesterol, LDL cholesterol, VLDL cholesterol, triglyceride and declined level of HDL cholesterol in STZ induced diabetic rats. STZ induced diabetic rats treated with different doses of α-mangostin significantly ($P < 0.001$) altered the lipid profile as compared to STZ induced diabetic rats.

3.9. *Effect of α-mangostin on atherogenic index and coronary risk index*

STZ induced diabetic control group rats showed the enhanced level of atherogenic index and coronary risk factor as compared to normal control and normal control group rats treated with α-mangostin 100 mg/kg (Table 8). STZ induced diabetic rats treated with α-mangostin showed the inhibition of atherogenic index and coronary risk factor at effective dose dependent manner.

3.10. *Effect of α-mangostin on renal function parameters*

As the evidence from Table 9 that untreated diabetic rats showed the increased level of BUN, serum creatinine and decreased level of total protein. STZ induced diabetic rats, orally treated with α-mangostin decreased the level of BUN, serum

Table 6 – Effect of α-mangostin on hepatic enzymes in normal & STZ induced diabetic treated rats.

S. No	Groups	Hepatic enzyme level		
		Hexokinase (μg/mg of tissue)	Glucose-6-phosphatase (unit/mg of tissue)	Fructose-1-6-biphosphatase (unit/mg of tissue)
1	Normal control	145.2 ± 1.934	8.8 ± 0.372	28.2 ± 0.882
2	Normal control + α-mangostin (100 mg/kg)	144.2 ± 1.319	9 ± 0.316	28.8 ± 0.281
3	Diabetic control	94.6 ± 1.327	13.6 ± 0.509	60.6 ± 0.748
4	α-Mangostin (25 mg/kg)	108.2 ± 1.855*	13 ± 0.261^{ns}	52 ± 1.923*
5	α-Mangostin (50 mg/kg)	122 ± 0.948***	11.8 ± 0.272**	40.4 ± 1.077**
6	α-Mangostin (100 mg/kg)	138.8 ± 1.497***	9.4 ± 1.021***	32.8 ± 0.862***
7	Glibenclamide (10 mg/kg)	135.4 ± 1.621***	9.8 ± 0.821***	36.2 ± 1.821***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin.
* $p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 7 – Effect of α-mangostin on lipid profile in normal & STZ induced diabetic treated rats.

S. No	Groups	Serum lipid profile				
		TC (mg/dL)	HDL (mg/dL)	TG (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
1	Normal control	78.8 ± 0.489	57.6 ± 0.812	82 ± 0.707	4.8 ± 0.839	16.4 ± 0.932
2	Normal control + α-mangostin (100 mg/kg)	78.8 ± 0.489	57.8 ± 1.068	82.2 ± 0.489	4.6 ± 0.932	16.4 ± 0.839
3	Diabetic control	129.4 ± 1.536	23 ± 0.707	138.2 ± 1.562	78.7 ± 1.292	27.64 ± 1.039
4	α-Mangostin (25 mg/kg)	107 ± 1.924*	30.2 ± 0.663**	128.2 ± 1.463*	51.1 ± 1.932**	25.64 ± 1.212ns
5	α-Mangostin (50 mg/kg)	95.2 ± 1.393**	38.8 ± 0.862***	110.2 ± 1.068**	34.36 ± 0.932***	22.08 ± 1.123**
6	α-Mangostin (100 mg/kg)	84.6 ± 0.927***	50.8 ± 1.165***	90.4 ± 1.721***	15.72 ± 0.728***	18.08 ± 0923***
7	Glibenclamide (10 mg/kg)	89.8 ± 0.663***	48 ± 1.517***	97 ± 1.143***	22.4 ± 0.128***	19.4 ± 1.029***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin, TC = Total Cholesterol, HDL = High density lipoprotein, TG = Triglyceride, LDL = Low density lipoprotein, VLDL = Very low density lipoprotein.
* $p < 0.05$ is considered as very significant when compared to the control group (0 h).
** $p < 0.01$ is considered as very significant when compared to the control group (0 h).
*** $p < 0.001$ is considered as extremely significant when compared to the control group (0 h).

creatinine and increased the level of total protein to a momentous level in STZ induced diabetic rats. The maximum improvement of renal parameters was observed in α-mangostin (100 mg/kg, body weight) treated group rats as compared to untreated diabetic rats and other doses received rats (Table 9).

3.11. *Effect of α-mangostin on hepatic function parameters*

SGOT, SGPT and ALP tests, measurement of hepatic function tests were performed during the experimentation. STZ induced

Table 8 – Effect of α-mangostin on artherogenic index and coronary risk index.

S. No	Groups	Artherogenic index	Coronary risk index
1	Normal control	0.08 ± 0.008	1.42 ± 0.083
2	Normal control + α-mangostin (100 mg/kg)	0.07 ± 0.006	1.41 ± 0.074
3	Diabetic control	3.42 ± 0.984	6.01 ± 1.252
4	α-Mangostin (25 mg/kg)	1.69 ± 0.221*	4.24 ± 0.938*
5	α-Mangostin (50 mg/kg)	0.88 ± 0.054**	2.84 ± .0738**
6	α-Mangostin (100 mg/kg)	0.31 ± 0.012***	1.78 ± 0.225***
7	Glibenclamide (10 mg/kg)	0.46 ± 0.029***	2.02 ± 0.431***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant.
* $p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 9 – Effect of α-mangostin on renal function parameters in normal & STZ induced diabetic treated rats.

S. No	Groups	Renal function parameters		
		Serum creatinine (mg/dl)	Total protein (g/dl)	BUN (mg/dl)
1	Normal control	0.84 ± 0.261	7.2 ± 0.374	31.6 ± 1.077
2	Normal control + α-mangostin (100 mg/kg)	0.86 ± 0.0254	7.2 ± 0.283	32.6 ± 0.927
3	Diabetic control	2.02 ± 0.932	3.6 ± 0.509	90.8 ± 2.059
4	α-Mangostin (25 mg/kg)	1.45 ± 0.283*	4.6 ± 0.593*	72.8 ± 1.356*
5	α-Mangostin (50 mg/kg)	1.21 ± 0.029**	5.8 ± 0.374**	54.4 ± 1.601**
6	α-Mangostin (100 mg/kg)	0.98 ± 0.0149***	7 ± 0.316***	36.4 ± 1.364***
7	Glibenclamide (10 mg/kg)	1.02 ± 0.0154***	6.7 ± 0.245***	38.2 ± 1.281***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin, BUN = Blood urea nitrogen.
* $p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 10 – Effect of α-mangostin on renal enzymes parameters in normal & STZ induced diabetic treated rats.

S. No	Groups	Liver enzymes parameters		
		SGOT (U/l)	SGPT (U/l)	ALP (IU/dl)
1	Normal control	123 ± 1.789	89.4 ± 1.077	128.6 ± 1.364
2	Normal control + α-mangostin (100 mg/kg)	123.4 ± 2.015	88.6 ± 1.043	126.4 ± 1.503
3	Diabetic control	212.4 ± 1.288	169.4 ± 2.043	282.9 ± 2.768
4	α-Mangostin (25 mg/kg)	193 ± 1.897*	142.8 ± 1.881*	210.1 ± 1.503*
5	α-Mangostin (50 mg/kg)	164.8 ± 2.131**	125 ± 1.643**	165.3 ± 2.956**
6	α-Mangostin (100 mg/kg)	141.4 ± 1.503***	95.2 ± 1.985***	138.2 ± 1.691***
7	Glibenclamide (10 mg/kg)	145.6 ± 1.887***	101.4 ± 1.536***	146.5 ± 1.158***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin, SGOT = Serum glutamic oxaloacetic transaminase, SGPT = Serum glutamic pyruvic transaminase, ALP = Alkaline phosphate.

* $p < 0.05$ is considered as very significant when compared to the control group.

** $p < 0.01$ is considered as very significant when compared to the control group.

*** $p < 0.001$ is considered as extremely significant when compared to the control group.

diabetic rats showed the increased activities of SGOT, SGPT and ALP. STZ induced diabetic rats treated with different doses of α-mangostin showed declined levels of SGOT, SGPT and ALP as compared to STZ induced untreated diabetic rats (Table 10). Oral administration of α-mangostin (25 mg/kg, 50 mg/kg and 100 mg/kg, body weight) brought the level of SGOT, SGPT and ALP near to normal control, similar to standard drug (glibenclamide).

3.12. *Effect of α-mangostin on antioxidant enzymes*

Table 11 showed the activities of endogenous antioxidant enzymes viz., SOD, CAT, LPO and GSH in the normal and STZ induced diabetic rats. There was significant ($P < 0.001$) enhancement in the level of LPO and reduction in the level of CAT, SOD, GSH was observed in STZ induced diabetic rats. STZ induced diabetic rats treated with α-mangostin (25, 50 and 100 mg/kg, p.o.) significantly ($P < 0.001$) restored the endogenous antioxidant enzymes value near the normal level.

3.13. *Effect of α-mangostin on CRP, TNF-α and IL-6*

Table 12 showed the effect of α-mangostin on CRP, TNF-α and IL-6. STZ induced diabetic control group rats showed the enhanced level of inflammatory cytokines viz., CRP, TNF-α and IL-6. Oral administration of α-mangostin significantly ($P < 0.001$) brought back the inflammatory level near to normal control level at dose dependent manner.

3.14. *Effect of α-mangostin on histopathology*

3.14.1. *Pancreas*

The normal control group rat histopathology demonstrated the normal architecture viz., average sized of islet of Langerhans were covered the pancreatic acini as well as prominent nuclei with arranged lobules covered by islet of Langerhans cells. STZ induced diabetic rats showed the completely damaged β cells, islets, acini, degeneration with asymmetrical vacuoles and ne-

Table 11 – Effect of α-mangostin on antioxidant enzymes in normal & STZ induced diabetic treated rats.

S. No	Groups	Antioxidant parameters			
		LPO (μmole of MDA/mg protein)	SOD (units/mg protein)	CAT (μmole of H_2O_2 consumed/min/mg of protein)	GSH (μmole of GSH/mg protein)
1	Normal control	7.6 ± 0.509	50.8 ± 1.881	74.4 ± 1.503	40.6 ± 1.208
2	Normal control + α-mangostin (100 mg/kg)	7.8 ± 0.372	50.6 ± 2.379	73 ± 1.225	39.6 ± 0.748
3	Diabetic control	17 ± 0.846	12.6 ± 0.927	48.4 ± 1.435	18.2 ± 1.145
4	α-Mangostin (25 mg/kg)	14 ± 0.316*	17 ± 1.581*	56.6 ± 1.288^{ns}	24.8 ± 0.583*
5	α-Mangostin (50 mg/kg)	12.2 ± 0.374**	31 ± 1.225**	64.4 ± 1.568**	30.2 ± 0.707***
6	α-Mangostin (100 mg/kg)	8.8 ± 0.372***	45.6 ± 1.691***	70.2 ± 0.861***	37.4 ± 1.327***
7	Glibenclamide (10 mg/kg)	9.4 ± 0.483***	43.2 ± 1.241***	68 ± 1.14***	36.8 ± 1.158***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, STZ = Streptozotocin, LPO = Lipid peroxidation, SOD = Superoxide dismutase, CAT = Catalase, GSH = Reduced glutathione;.

* $p < 0.05$ is considered as very significant when compared to the control group.

** $p < 0.01$ is considered as very significant when compared to the control group.

*** $p < 0.001$ is considered as extremely significant when compared to the control group.

Table 12 – Effect of α-mangostin on serum TNF-a, IL-6 and CRP of normal & STZ induced diabetic treated rats.

S. No	Groups	Parameters		
		CRP (ng/ml)	IL-6 (pg/ml)	TNF-α (pg/ml)
1	Normal control	6369 ± 280	35.6 ± 1.17	162.4 ± 8.19
2	Normal control + α-mangostin (100 mg/kg)	6228 ± 471.6	35.2 ± 0.86	163 ± 9.33
3	Diabetic control	11837 ± 1437	57.8 ± 1.59	248.4 ± 16.72
4	α-Mangostin (25 mg/kg)	11452 ± 1059*	50.6 ± 2.99ns	236.2 ± 14.43*
5	α-Mangostin (50 mg/kg)	9424 ± 696.6***	44.2 ± 1.28*	198.8 ± 13.85**
6	α-Mangostin (100 mg/kg)	6402 ± 305.2***	36 ± 0.55***	166.6 ± 9.54***
7	Glibenclamide (10 mg/kg)	6603 ± 186.3***	37.4 ± 1.03***	175 ± 10.6***

The data are expressed as mean ± SEM. (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnett's test. ns = non-significant, TNF-α = Tumor necrosis factor α, CRP = C-reactive protein, IL-6 = Interleukin 6;.
* $p < 0.05$ is considered as very significant when compared to the control group.
** $p < 0.01$ is considered as very significant when compared to the control group.
*** $p < 0.001$ is considered as extremely significant when compared to the control group.

crosis changes which was followed by atrophy and fibrosis. STZ induced diabetic rats treated with α-mangostin showed the improvement of marked cellular injury as well as enhanced restoration of islet cells, producing the protective effect for β cells and more asymmetrical vacuoles (Fig. 11).

3.14.2. *Liver*

Histopathology study of normal control group rats showed the average sized hepatocytes with central vein along with threshold triad. STZ induced diabetic rats liver histopathology showed the damage of hepatocytes taken over macro

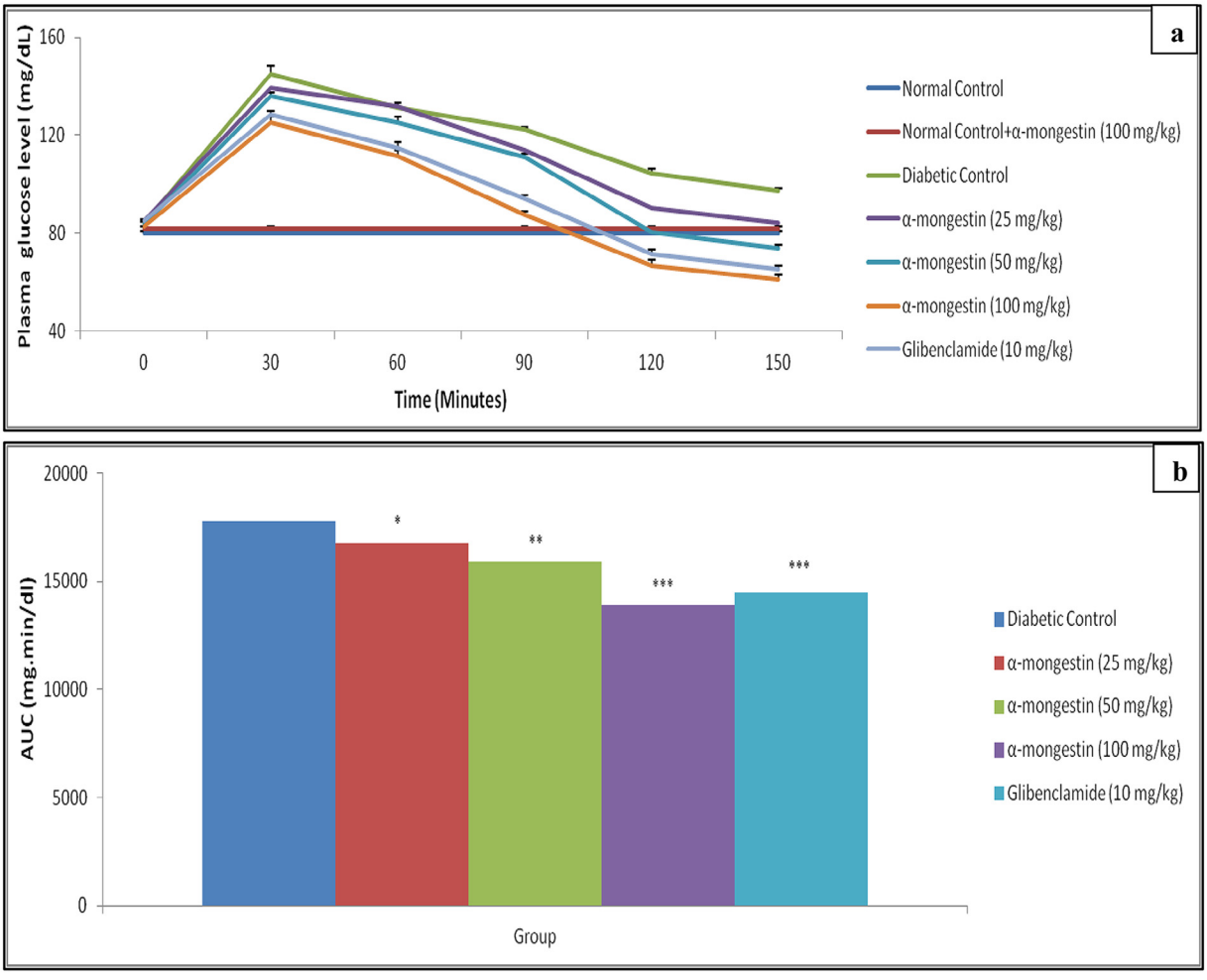

Fig. 11 – Oral glucose tolerance and AUC of α-mangostin in glucose-hyperglycemias animal model rats. Values are given as mean ± S.E.M. of six rats in each group. *p ≤ 0.05, **p ≤ 0.005, ***p ≤ 0.001 compared with normal control values.

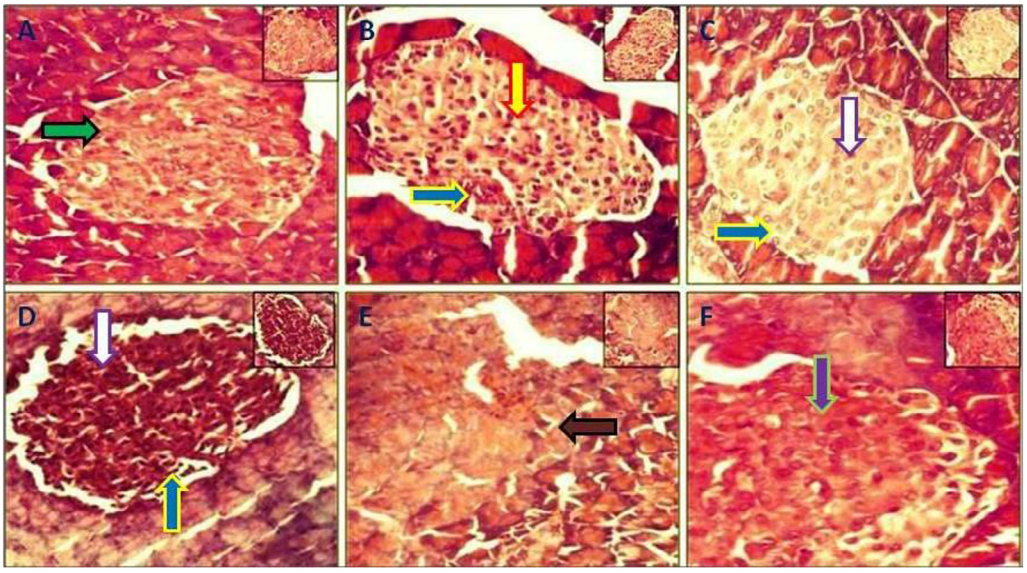

Fig. 12 – The effect of α-mangostin on pancreas histopathology in normal and STZ induced diabetic rats. (Original magnification 40× , DXIT 1200, Nikon, Japan). (A) **Normal control: Normal control group displays the average sized β cells and normal islets (green arrow).** (B) **Diabetic Control: diabetic control rats pancreata histopathology showing the small sized dilated and degranulated islet cells (yellow arrow) without amplification of the β cells (blue arrow).** (C) **Diabetic + α-mangostin (25 mg/kg): treated rat pancreata showing the islets with endocrine cells, increasing more exocrine acini and cytoplasm (white arrow) with enhancing of the sized of β cells (blue arrow).** (D) **Diabetic + α-mangostin (50 mg/kg): treated rat pancreata showing the prominent hyper plasticity islet, granulated pancreatic islets (white arrow) and with enhancing of the sized of β cells (blue arrow)** (E) **Diabetic + α-mangostin (100 mg/kg): treated rat pancreata showing the enlargement of the β-cells with pink granules in the cytoplasm (brown arrow).** (F) **Diabetic + glibenclamide (10 mg/kg): treated rat pancreata histopathology showing the hyper plasticity of islets and nonappearance, granulated islets with enlargement of (purple arrow).**

droplet of fats and accumulation of fats. STZ induced diabetic rats treated with α-mangostin showed the improvement of hepatocytes as well as central vein and reduced the accumulation of fat droplets over the hepatocytes and improve the liver cells (Fig. 12).

3.14.3. *Renal*

Renal histopathology studies of normal control and diabetic control showed the significant difference in respect to tubular dilation, focal necrosis (glomerulus), consolidation of the vascular wall and tubular epithelial necrosis. A significant difference was observed in diabetic control group and α-mangostin group as for decreasing the glomerulus focal necrosis; decrease the size of bowman capsules, consolidation of the vascular wall, tubular epithelial necrosis (Figs. 13 and 14).

4. Discussion

Diabetes Mellitus (DM) is a deadly disease, consisting of chronic disorder of carbohydrate, protein, fat, and lipid metabolism characterized by hyperglycemia resulting from the defects of insulin action, insulin secretion, macrovascular (Stroke, heart attack and vascular disease) and microvascular (Nephropathy, retinopathy and neuropathy) complications (Badole and Bodhankar, 2010; Irudayaraj et al., 2012).

An increased blood glucose level in glycemic rats and glycemic rats treated with α-mangostin rats were observed in oral glucose tolerance test (OGTT). The level of plasma insulin was increased in the normoglycemic rats, while it was not changed in glycemic rats in OGTT. Oral administration of α-mangostin (25, 50 and 100 mg/kg) and glibenclamide significantly ($P < 0.001$) decreased the blood glucose level with changed plasma insulin level. The possible mechanism action of α-mangostin on hypoglycemic effect may be involved its insulin like effects. α-Mangostin increased the activity of pancreatic β-cells, resulting in enhanced secretion of large amounts of insulin which in turn brought down the blood glucose level (Nain et al., 2012). From the result, it is assumed that α-mangostin could be responsible for the prompt for insulin and restoration of metabolic activity.

STZ induced diabetic rats showed the effect on blood glucose and insulin level due to abnormalities of β cell function (Strandell et al., 1988). STZ induced diabetic rats treated with different doses of α-mangostin declined the blood glucose level and improved the plasma insulin level at dose dependent manner (Table 3). Glibenclamide stimulated the plasma insulin secretion from the pancreatic β cells and the blood glucose level declined. STZ induced diabetic rats treated with different doses of α-mangostin and glibenclamide had significantly ($P < 0.001$)

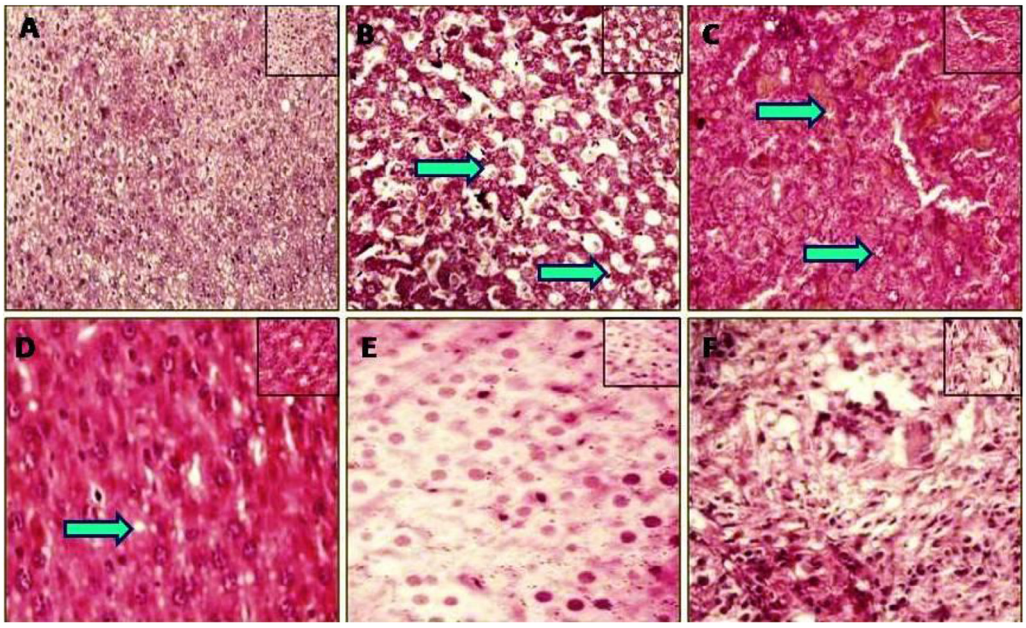

Fig. 13 – The effect of α-mangostin on liver histopathology study in STZ induced experimental rats after 56 days of treatment. (Original magnification 40× , DXIT 1200, Nikon, Japan). (A) **Normal control—Normal control group rats liver showing the normal architecture and hepatic cells.** (B) **Diabetic control: diabetic control rats histopathology clearly showing the hepatocellular necrosis and extensive vocalization with the vanishing of nuclei with disordered of the liver structure (green arrow).** (C) **Diabetic + α-mangostin (25 mg/kg): treated rats showing the fibrotic changes, hepatocellular necrosis and fat deposition (green arrow)** (D) **Diabetic + α-mangostin (50 mg/kg): treated rats showing the fat deposition, fibrotic changes and the hepatocellular necrosis (green arrow)** (E) **Diabetic + α-mangostin (100 mg/kg): treated rats showing the normal nucleus, cytoplasm and hepatocellular architecture.** (F) **Diabetic + glibenclamide (10 mg/kg): treated rats showing the distinct hepatic layer, cytoplasm and normal heptocellular architecture.**

declined plasma blood glucose level and improved pancreatic β cells. Based upon the result, probable mechanism of action of α-mangostin may be to act on pancreatic β cells and start the secretion of insulin. This hypothesis was confirmed by histopathology study of STZ induced diabetic rats treated with α-mangostin which showed the protection of pancreatic β cells from the toxic effect of STZ (Fig. 12).

STZ induced diabetic rats showed the increased level of blood glucose and declined level of plasma insulin at the end of the study. STZ induced diabetic rats treated with α-mangostin and glibenclamide showed the enhanced level of plasma insulin. Based upon the result, it can be hypothesized that α-mangostin and glibenclamide showed the protective effect of pancreatic β cells against the toxin (STZ) (Kumar et al., 2013a, 2013b, 2013c). This hypothesis was confirmed by a pancreatic histopathology study of STZ induced diabetic rats treated with α-mangostin and glibenclamide. The histopathology study showed the number of β cells did not increased but the size of present β cells increased (Fig. 11).

Diabetes Mellitus is associated with weight loss. STZ induced diabetic rats showed the body weight loss. The decreased level of body weight was characterized by degradation of structural proteins and increased muscle destruction (Nain et al., 2012). STZ induced diabetic rats treated with different doses of α-mangostin and glibenclamide reversals of weight loss indicated the restorative effect of α-mangostin. The possible mechanism of action of α-mangostin may be due to reversal of proteolysis, glycogenolysis and gluconeogenesis.

Type I and Type II diabetes often involve lipid metabolism abnormality which is a metabolic disorder condition with diabetic complications viz., atherosclerosis, hypertriglyceridemia, hypertension and hypercholestermia, which may contribute to coronary artery diseases (Ferrannini et al., 1987; Krentz, 2003; Zavaroni et al., 1987). Serum triglyceride and total cholesterol level increased in hyperglycemia and produced the lipid abnormality; lipid abnormality caused the glucose intolerance (developing the diabetes) (Kumar et al., 2012). Under normal conditions, insulin activates the lipoprotein lipase, which hydrolyzes the triglycerides. The level of triglyceride increased due to insulin deficiency, resulting it unable to activate the lipoprotein lipase and causes the hypertriglyceridemia. (Kumar et al., 2014). Under normal circumstances, HDL excretion from the peripheral tissue. The increased level of LDL and VLDL starts the cholesterol deposition in peripheral tissue and decreased level of HDL not excreted from the peripheral tissue. Hence, increased level of HDL and decreased level of VLDL produce the atherogenic conditions (Ahmed et al., 2013). STZ induced diabetic rats treated with α-mangostin significantly ($P < 0.001$) brought back the lipid profile near to normal condition. The possible mechanism of action of α-mangostin may be to augment the level of insulin, which increases the utilization of glucose, inhibits the hormonal sensitivity of lipase;

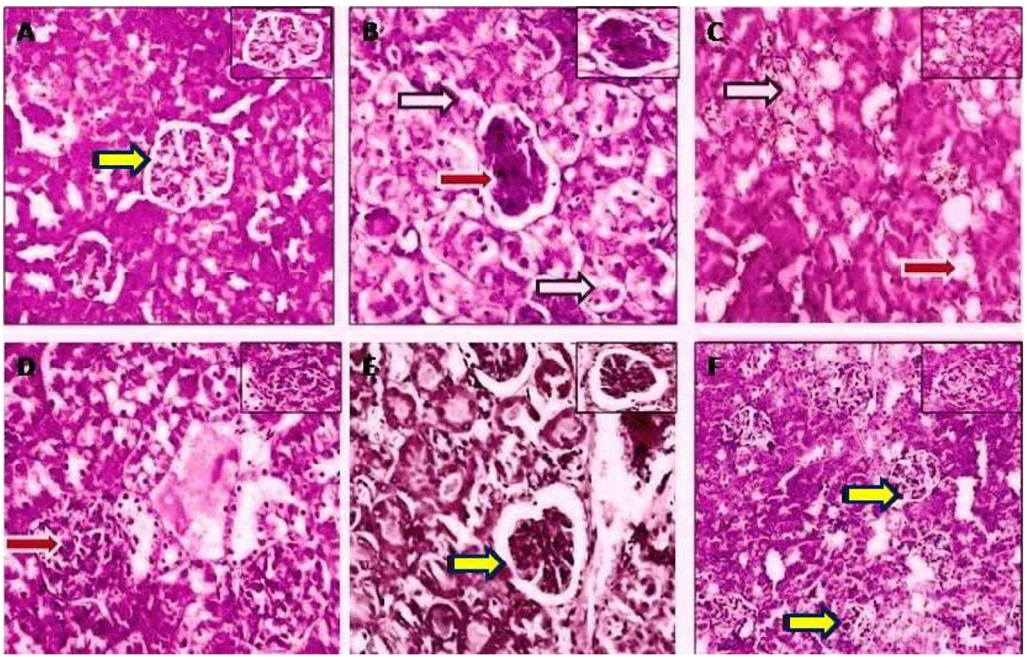

Fig. 14 – The effect of α-mangostin on kidney histopathology in normal and STZ induced diabetic rats. (Original magnification 40× , DXIT 1200, Nikon, Japan). (A) **Normal control: normal control rat kidney histopathology showing the average size of glomerulus with an average size of tubulus, baseline and average sizes of bowman capsule (yellow arrow).** (B) **Diabetic Control: diabetic control rats showing the destroyed glomerulus with deposition of fats on baseline and served the glomerulosclerosis, bigger size of bowman capsule (red arrow) and inflamed blood vessels, lymphocytes (white arrow).** (C) **Diabetic + α-mangostin (25 mg/kg): treated rat kidney showing the inflamed blood vessels (white arrow) and fat deposition (red arrow).** (D) **Diabetic + α-mangostin (50 mg/kg): treated rat kidney showing the fat deposition with less inflamed blood cells (red arrow).** (E) **Diabetic + α-mangostin (100 mg/kg): treated rat kidney showing the average size of glamorous without inflammation in blood vessels and enhance the tubule structure.** (F) **Diabetic + glibenclamide (10 mg/kg): treated rat kidney histopathology showing the average size of glomerulus without inflammatory blood vessels.**

and declines the deposition of fatty acids. The atherogenic index and coronary risk factor also efficient protector of lipid lowering therapy. This hypothesis was confirmed by the liver histopathology studies of α-mangostin treated groups (Fig. 5).

Liver is an important organ, which plays an important role in the synthesis of glycogen and protection of postprandial hyperglycemia (Kumar et al., 2013a, 2013b, 2013c). Constant hyperglycemia is leads to development of many complications during diabetes, such as neuropathy and microvascular (Laakso et al., 1995). In normal circumstances, liver plays an important role in the ruling of glucose metabolizing enzymes viz., hexokinase, glucose-6-phosphatase and fructose-1-6-biphosphate. Several studies confirmed that the reduced level of fructose-1-6-biphosphate, glucose-6-phosphatase and enhanced level of hexokinase observed during the diabetes condition, same was observed in the current study. Hexokinase is one of the most important enzyme which plays an important role in conversion of glucose into glucose-6-phosphatase (Baquer et al., 1998; Latha and Pari, 2003). Declined level of hexokinase, decreases the conversion of glucose into glucose-6-phosphatase and utilization of energy. Glucose-6-phosphatase regulates the glucose metabolizing enzymes. STZ induced diabetic rats showed the increased level of glucose-6-phosphatase which declined the glucose metabolizing enzymes and enhanced the fat deposition in liver (Liu et al., 1994). The deposition of fats in liver has been supported by histopathology studies of STZ induced diabetic rats. Fructose-1-6-biphosphate is another enzyme which takes part in the conversion of glucose into energy and glycolysis (Kumar et al., 2014). The possible mechanism action of α-mangostin may be increasing the insulin level, which improves the glycolysis and declines the gluconeogenesis.

The increase level of free radicals causes the hyperglycemia, followed by production of oxidative stress, which can increase the level of lipid oxidation, alter endogenous antioxidant defense and further impairment of glucose metabolism in biological system (Bansala et al., 2012). Oxidative stress, initiating to decrease the endogenous antioxidant status and improper control of deleterious effects of free radicals, plays an important role in the macrovascular and microvascular condition during diabetes (Ceriello et al., 2000). During the oxidative stress, reduction of superoxide radical (O_2) and hydrogen peroxide radical (H_2O_2) are playing an important role in cellular, tissue damaging and causing a variety of diabetes conditions. DM conditions and endogenous antioxidant levels were decreased and start damaging organ due to generation of oxidative stress by free radicals (Memişoğullari and Bakan, 2004). SOD and CAT, is the first line endogenous scavenging enzymes that remove or decrease the level of free radicals. SOD and CAT content decreased in liver, kidney and pancreas during the diabetes mellitus. The declining level of free radicals in vital organs,

starts the accumulation of superoxide, hydrogen peroxide anion and starts the generation of delicious radicals such as hydroxyl (OH), resulting in the spreading of lipid peroxidation (LPO). LPO is one of the common characteristic features of diabetes mellitus. Continuous production of free radicals such as superoxide and hydrogen peroxide starts peroxidation of unsaturated free fatty acids and damaging the tissue and attacking the membranes (Balasubashini et al., 2004; Ravi et al., 2004). Continuous generation of free radicals can lead to increased level of LPO, increased levels of LPO damage the membrane and cause dysfunction (Alfy et al., 2005). On the other hand, increased production of superoxide decreased the level of LPO. STZ induced diabetic rats treated with α-mangostin and showed enhanced levels of LPO as compared to diabetic rats. Levels of SOD and CAT in the organ decreased due to activation of glycation by enzymes (Yan and Harding, 1997). SOD plays an important role in the conversion of the delicious anions like superoxide into hydrogen peroxide, which showed the effect on the damaging membrane and biological structures. Another first line antioxidant such as CAT, convert the hydrogen peroxide into hydroxyl radicals and protect the tissue from highly reactive hydroxyl radicals. STZ induced diabetic rats treated with different doses of α-mangostin significantly ($P < 0.001$) increased the level of hepatic and renal SOD, CAT and claimed the antioxidant effect of α-mangostin. Transitional metal reacts with peroxide and generate the delicious hydroxyl radical (Halliwell and Gutteridge, 1999). The increased level of SOD; increased the level of GPx and showed the overload of peroxide in the cells. The possible mechanism of action of α-mangostin may be due to declined levels of reactive free radicals, which either reduced the glycation of enzymes or enhanced the level of endogenous antioxidant levels. The result clearly showed that α-mangostin contains the free radical scavenging activity, which could be a beneficial action against the hydrogen peroxide, hydroxyl and superoxide radicals, which caused the pathological alteration.

The storage of glucose in the form of intracellular storable, glycogen plays an important role in the storage of glucose. Diabetes mellitus shows the effect on liver of impairment of the normal capacity to synthesize glycogen (Pandit et al., 2010). In normal conditions, insulin activates the intracellular glycogen storage by inhibiting the glycogen phosphorylase and enhancing the synthesis of glycogen (Chandramohan et al., 2008). Declined levels of hepatic glycogen were observed in STZ induced diabetic rats. STZ induced diabetic rats treated with α-mangostin showed the significantly ($P < 0.001$) enhanced the level of hepatic glycogen indicating the improved of the glycogen storage in diabetic condition.

In normal circumstances, small volume of blood glucose and 3.4–5.8% of hemoglobin has been covalently bonded to red blood cells in hemoglobin. During diabetes production of free radicals and blood glucose level in blood are increased. Glycation is directly propositional to hyperglycemia. Some of researcher claim that the increased rate of blood glucose, which increased the glycation and glycation itself increased the generation of free radicals during the diabetes conditions. Glycated hemoglobin used as a marker of oxidative stress during the diabetic conditions (Bravi et al., 2006). During the diabetic condition, level of glycated hemoglobin is increased due to enhanced blood glucose. Enhanced level of blood glucose starts by adding the hemoglobin in N terminus and improving the level of glycated hemoglobin (Klujber et al., 1979). STZ induced diabetic rats showed the increased level of glycated hemoglobin at end of the experiment. STZ induced diabetic rats treated with α-mangostin showed the level of glycated hemoglobin has decreased. The possible mechanism of action of α-mangostin may be due to decline in the blood glucose level and enhancement in the endogenous antioxidant level.

Liver is a vital organ of body for detoxification, metabolism, storage of xenobiotics and their metabolites. SOGT, SGPT and ALP are the biological markers of liver function. During the diabetes condition, SGOT, SGPT and ALP levels are increased due to the release of these enzymes into the liver cytosol from the blood stream (Mahendrn et al., 2014). These hepatic marker released into the blood stream showed the hepatic toxic effects (Ramesh et al., 2010). STZ induced diabetic rats showed the increased level of hepatic marker and showed the hepatic toxicity. STZ induced diabetic rats treated with α-mangostin showed the systematic declined level of hepatic markers and confirmed the hepato-protective effect of α-mangostin. The possible mechanism of action of α-mangostin may be due to decline in the blood glucose level and hepatic biomarker. This hypothesis was confirmed from the liver histopathology studies. The diabetic liver histopathology showed the necrosis and inflamed blood vessels, which are improved in α-mangostin treated group rats at effective dose dependent manner.

STZ induced diabetic rats showed the enhanced level of creatinine, BUN and declined level of total protein as comparison to normal control group rats. Enhanced level of creatinine, BUN and declined level of total protein showed the renal dysfunction. Some researchers claim that the increased level of creatinine and BUN are waste products of metabolism and causes the renal injury or toxicity. Enhanced level of creatinine and BUN due to degradation of protein and decreasing the glamor filtration rate (Ahmed et al., 2014, 2015). In our study, STZ induced diabetic rats treated with α-mangostin showed the declined level of creatinine, BUN and enhanced level of total protein. The possible mechanism of action of α-mangostin may be declined by the degradation of protein. We observed the less focal necrosis and tubular epithelial necrosis in the renal histopathology of treated group, which provide the support to our hypothesis. (Fig. 12).

Inflammation plays an important role in the expansion of type II diabetes and reduced the insulin sensitivity. Inflammatory markers such as CRP and TNF-α are circulating markers of low grade inflammation and vascular injury. The elevated level of CRP is linked with glucose tolerance, obesity, and insulin resistance; increased level of CRP also involved in the increasing the blood glucose level and the etiology of type II diabetes (Hu et al., 2004). Generally, CRP produced and secreted from the liver under the encouragement of cytokines such as IL-6 and TNF-α. IL-6 showed the effect on insulin induced glucose by altering insulin receptor, glut-4 and IRS, which starts the expansion and progression of insulin resistance (Khan et al., 2013). In our experimental study, levels of CRP, TNF-α and IL-6 significantly increased and showed the symptoms of type II diabetes. STZ induced diabetic rats treated with α-mangostin showed the marked alteration in the level of the serum cytokine. The level of the IL-6 and CRP declined by the treatment with

α-mangostin showed the reduction in the insulin resistance. The possible mechanism of action of α-mangostin may be due to increased level of the cytokine mediators and provide the anti-inflammatory effect (Ramprasath et al., 2006).

5. Conclusion

A significant improvement in the insulin, hemoglobin, hexokinase, endogenous antioxidant enzymes, renal parameters, hepatic enzymes, lipid profile and declining level of glycated hemoglobin, fructose-1-6-biphosphatase, glucose-6-Phosphatase were observed among STZ induced diabetic rats treated with α-mangostin. It is thus concluded that α-mangostin is a promising antidiabetic, antihyperlipidemic, hepatoprotective, renal protective, free radical scavenger compound. α-Mangostin also improved the various abnormalities of diabetic conditions in the STZ induced diabetic rats. The mode of action of α-mangostin may depend on the many factors viz., animal (age, sex, health, time of treatment), drug (concentration), route of administration (oral gavage, injection, supplement), and diabetic model used. As we have already discussed, at different doses, α-mangostin can either act to improve the insulin level or act as a free radical scavenger by increasing the activity of endogenous antioxidant enzymes, and possibly act through a novel mechanism of action yet to be discovered.

It can be concluded that α-mangostin could be used in the clinical management of diabetes. The therapeutic effects of α-mangostin can be endorsed to their action on insulin resistance, oxidant–antioxidant system, hyperlipidemia, renal, hepatic and inflammation process.

Acknowledgments

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List of abbreviations

STZ	streptozotocin
OGTT	oral glucose tolerance test
CRE	creatinine
BUN	total blood urea nitrogen
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ALP	alkaline phosphatase
TC	total cholesterol
TG	triglycerides
HDL	high density lipoprotein
LDL	low density lipoprotein
VLDL	very low density lipoprotein
LDL	lipid peroxidation
SOD	superoxide dismutase
CAT	catalase
GSH	reduced glutathione
CPR	C-reactive protein
TNF-α	tumor necrosis factor
DM	diabetes mellitus
ROS	reactive oxygen species
WHO	World Health Organization
iPH	ponderal homogeneity index
PG	ponderal grain
AUC	area under control
OH	hydroxyl
CMC	carboxyl methyl cellulose

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