Impact of Bitter Gourd (*Momordica charantia*) Hypoglycemic Formulation on Biochemical Parameters in Alloxan-Induced Diabetic Albino Rats

Abstract

Introduction

Diabetes mellitus is a widespread endocrine disorder that leads to chronic hyperglycemia, posing significant health challenges globally. Effective management of blood glucose levels remains a critical goal in diabetes treatment. Recent studies have highlighted the potential of natural products in diabetes management. *Momordica charantia*, commonly known as bitter gourd, has been traditionally used for its purported hypoglycemic effects. This study aims to evaluate the efficacy of a methanolic extract of *Momordica charantia* in reducing blood glucose levels in an animal model of diabetes and compare its effectiveness to a standard antidiabetic medication, Glizid-M.

Materials and Methods

The study utilized alloxan-induced diabetic albino rats to assess the hypoglycemic effects of the methanolic extract of *Momordica charantia*. Diabetic rats were divided into groups and administered varying doses of the extract: 150 mg/kg, 300 mg/kg, and 600 mg/kg. A control group received Glizid-M, and a baseline group received no treatment. Blood glucose levels were monitored at regular intervals to evaluate the efficacy of the extract in managing hyperglycemia.

Results and Discussion

The administration of the methanolic extract of *Momordica charantia* resulted in a dose-dependent reduction in blood glucose levels. Among the tested dosages, the 600 mg/kg dose demonstrated a statistically significant decrease in blood glucose compared to the lower doses of 150 mg/kg and 300 mg/kg. The 600 mg/kg dosage showed comparable efficacy to the standard antidiabetic drug, Glizid-M, indicating a strong hypoglycemic effect.

The results of this study suggest that *Momordica charantia* has a potent hypoglycemic effect, with its efficacy increasing with dosage. The significant reduction in blood glucose levels at the highest dosage implies that the extract may influence glucose metabolism effectively. The dose-dependent response highlights the importance of optimizing dosage for maximum therapeutic benefit. Comparison with Glizid-M further supports the potential of *Momordica charantia* as a viable alternative or complementary therapy in diabetes management.

Conclusion

This study provides scientific validation for the use of *Momordica charantia* methanolic extract as a therapeutic agent for diabetes management. The observed dose-dependent reduction in blood glucose levels suggests its potential as an effective natural remedy for controlling hyperglycemia. Further research is warranted to explore the underlying mechanisms and long-term efficacy of this extract in diabetes treatment.

Keywords: Diabetes Mellitus, Alloxan-Induced Diabetes, *Momordica charantia*, Hypoglycemic Activity, Blood Glucose Regulation

Introduction

"Diabetes Mellitus (DM) represents a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The two primary forms of diabetes are Type 1 Diabetes Mellitus (T1DM), formerly known as insulin-dependent diabetes mellitus (IDDM), and Type 2 Diabetes Mellitus (T2DM), formerly referred to as non-insulin dependent diabetes mellitus (NIDDM). Both types of diabetes have profound implications for health, leading to significant metabolic abnormalities such as dysregulated lipogenesis and protein glycosylation. The long-term complications associated with diabetes include cardiovascular disease, peripheral vascular disease, retinopathy, neuropathy, and nephropathy, all of which contribute to increased morbidity, mortality, and premature mortality, particularly among young adults. Additionally, diabetes can exacerbate reproductive issues, affecting both maternal and neonatal health" (American Diabetes Association, 2021).

In India, the prevalence of diabetes is projected to increase dramatically, with estimates suggesting a rise of 195% by 2025 (King et al., 1998). This escalating epidemic impacts both urban and rural populations, imposing significant social, psychological, and financial burdens (Mohan et al., 2006). Effective management of diabetes has traditionally focused on pharmacological interventions aimed at controlling blood glucose levels and mitigating associated complications (Tiwary and Madhusudana, 2002). Recent advances have refined therapeutic regimens, but the quest for novel and complementary treatment options continues.

Herbal remedies have gained traction as potential adjuncts to conventional diabetes therapies, due to their accessibility, cost-effectiveness, and lower side-effect profiles. Among these, *Momordica charantia* (bitter gourd), a member of the Cucurbitaceae family, has been extensively studied for its anti-diabetic properties. In India and several other Asian countries, bitter gourd is not only a staple vegetable but also a traditional remedy for diabetes (Garau et al., 2003; Chandrashekar et al., 1989). Clinical trials suggest that its aqueous extract may offer superior efficacy compared to dried powder or dietary consumption (Karumanayake et al., 1990; Ahmed et al., 2004).

"Momordica charantia influences glucose metabolism through multiple mechanisms. It has been shown to lower blood glucose levels by inhibiting disaccharidase enzymes, which prevents the hydrolysis of disaccharides into glucose" (Oishi et al., 2007; Kumar Shetty et al., 2005). "Additionally, it affects glucose transport channels, thereby reducing glucose absorption into the bloodstream" (Singh et al., 2004). These effects are beneficial for both T1DM and T2DM patients, aiding in the prevention of postprandial hyperglycemia.

In T1DM, characterized by autoimmune destruction of pancreatic β-cells leading to insufficient insulin production, *Momordica charantia* has been reported to enhance insulin secretion (Yibchok-Anun et al., 2006; Fernandes et al., 2007). Evidence suggests the presence of an insulin-like molecule within bitter gourd (Khanna et al., 1981). While bitter gourd can supplement insulin therapy, it does not replace the need for insulin administration entirely.

For T2DM, often associated with obesity and characterized by insulin resistance in the liver, skeletal muscle, and adipose tissue, *Momordica charantia* has demonstrated potential in reversing insulin resistance (Nerurkar et al., 2008; Klomann et al., 2010). Its consumption may also mitigate secondary complications such as

hypertension, dyslipidemia, and oxidative stress, which are common in T2DM patients (Satishekhar and Subramanian, 2005; Klomann et al., 2010). Furthermore, bitter gourd's impact on weight management and its potential anticancer properties add to its therapeutic appeal (Nerurkar et al., 2008). Thus, the growing body of evidence underscores the significance of *Momordica charantia* as a promising candidate for diabetes management, warranting further exploration to substantiate its efficacy and integrate it into broader therapeutic strategies.

Glizid-M: Mechanism of Action and Clinical Use-Glizid-M is a combination drug used in the management of type 2 diabetes mellitus. It combines two antidiabetic agents: glimepiride and metformin. This combination is designed to improve glycemic control through complementary mechanisms of action. Below is a detailed explanation of each component's mechanism and their combined therapeutic effects.**[1]. Glimepiride**-Glimepiride is a sulfonylurea drug that works primarily by stimulating insulin secretion from pancreatic beta cells. The key mechanisms include: -**Stimulation of Insulin Secretion:** Glimepiride binds to the sulfonylurea receptors (SUR1) on the surface of pancreatic beta cells. This binding leads to the closure of ATP-sensitive potassium channels, causing membrane depolarization. The depolarization opens voltage-gated calcium channels, resulting in an influx of calcium ions. The increase in intracellular calcium triggers the release of insulin from beta cells (Schulz et al., 2004). **Enhanced Insulin Sensitivity:** Beyond stimulating insulin release, glimepiride also improves peripheral insulin sensitivity, although this effect is less pronounced than that of metformin (Vella et al., 2000).**[2]. Metformin**-Metformin is a biguanide that primarily acts by improving insulin sensitivity and reducing hepatic glucose production. Its mechanisms include: **Reduction of Hepatic Glucose Production:** Metformin decreases the production of glucose in the liver by inhibiting hepatic gluconeogenesis. This action helps lower blood glucose levels independently of insulin secretion (Rena et al., 2017). **Improvement of Insulin Sensitivity:** Metformin enhances insulin sensitivity in peripheral tissues, facilitating better glucose uptake by cells. This effect is mediated through the activation of AMP-activated protein kinase (AMPK), which improves the cellular response to insulin (Zhou et al., 2001). **Reduction of Intestinal Glucose Absorption:** Metformin may also reduce the absorption of glucose from the gastrointestinal tract, though this effect is secondary compared to its other mechanisms (Cusi, 2016).

Combined Therapeutic Effects-The combination of glimepiride and metformin in Glizid-M leverages the distinct mechanisms of each drug to provide more comprehensive glycemic control: **Synergistic Effect:** While glimepiride enhances insulin secretion, metformin improves insulin sensitivity and reduces glucose production from the liver. This synergy helps achieve better control of blood glucose levels compared to using either drug alone. **Reduction of Dose-related Side Effects:** The combination allows for lower doses of each medication, potentially reducing the risk of side effects associated with higher doses of either agent alone (American Diabetes Association, 2019).

This detailed explanation of Glizid-M provides insight into the mechanisms of action of its components and their combined benefits in managing type 2 diabetes mellitus.

1. Materials and Methods

2.1 Plant Materials

The whole fruit of *Momordica charantia* Linn. (bitter gourd) utilized in this study was procured from a local vegetable market in Darbhanga, Bihar, India. Identification and authentication of the plant material were conducted by the Department of Botany, L. N. Mithila University, Darbhanga, Bihar, India.

2.2 Methanolic Extraction of Bitter Gourd Slices

The bitter gourd was thoroughly cleaned and sliced. The slices were air-dried at ambient temperature before being pulverized into a coarse powder. One kilogram of this coarse powder was subjected to methanolic extraction using a Soxhlet apparatus. The methanol extract was then concentrated under reduced pressure and subsequently dried in a vacuum desiccator to obtain the final extract.

2.3 Experimental Animals

Albino rats (weighing 100-150 g) of both sexes were procured from a local animal supplier in Darbhanga, Bihar, India. Prior to the commencement of experiments, the rats were acclimatized for seven days under controlled hygienic conditions and were provided with a standard rodent pellet diet (Gold Mohar, Lipton India Ltd.).

2.4 Oral Glucose Tolerance Test (OGTT)

After a 30-day treatment with the methanolic extract of bitter gourd, an oral glucose tolerance test (OGTT) was performed. The rats were fasted for 14-16 hours before administering an oral glucose load (2 g/kg) as described by Du Vigneaud and Karr (1925) and Al Awadi et al. (1985). Blood glucose levels were measured at 30, 60, 90, and 120 minutes post-glucose administration using the tail puncture method. Blood glucose concentrations were quantified using a glucometer (Dr. Morepen Gluco One, Delhi).

2.5 Acute Oral Toxicity of Bitter Gourd

The acute oral toxicity of the bitter gourd extract was evaluated by administering doses ranging from 2500 to 3000 mg/kg body weight to different groups of rats (8 rats per group). Mortality was monitored over a 24-hour period. Acute oral toxicity was assessed following the methodology described by Litchfield and Wilcoxon (1949).

LIST 1: Experimental Design

A total of six groups of albino rats, each consisting of eight rats, were subjected to the following treatment regimens:

• **Group A**: Normal Control
• **Group B**: Alloxan-treated control (150 mg/kg, i.p. body weight)
• **Group C**: Alloxan (150 mg/kg, i.p. body weight) + Bitter gourd extract (150 mg/kg body weight, oral treatment)
• **Group D**: Alloxan (150 mg/kg, i.p. body weight) + Bitter gourd extract (300 mg/kg body weight, oral treatment)

• **Group E**: Alloxan (150 mg/kg, i.p. body weight) + Bitter gourd extract (600 mg/kg body weight, oral treatment)
• **Group F**: Alloxan (150 mg/kg, i.p. body weight) + Glizid-M (standard drug, 5 mg/kg body weight, oral treatment)

Bitter gourd extract and the standard drug Glizid-M were administered via intubation. Group A served as the normal control, while Groups B through F consisted of diabetic rats. Groups C to F, having previously received alloxan, were treated with fixed doses of bitter gourd extract (150, 300, and 600 mg/kg body weight) and the standard drug Glizid-M for 30 days.

2.6 Induction of Diabetes in Experimental Animals

1. Diabetes was induced in rats through a single intraperitoneal injection of alloxan-monohydrate (150 mg/kg body weight) as per the protocol outlined by R.V. Aruna et al. (1999). Alloxan was weighed individually for each animal, dissolved in 0.5 ml of saline immediately before administration. After 72 hours, rats exhibiting elevated blood glucose levels (>290 mg/dl) were selected. Treatment commenced immediately, excluding the normal control and diabetic control groups. Throughout the study, all experimental animals were provided with standard hygienic water and pellet diet. *Alloxan is a toxic glucose analogue that selectively destroys pancreatic β-cells, resulting in insulin-dependent diabetes mellitus, similar to Type 1 diabetes in **humans** (Lenzen, 2008)*

2.7 Differences Between Healthy and Alloxan-Diabetic Rats

Healthy Rats

- The pancreas contains functional islets of Langerhans that regulate blood glucose levels.
- Following the ingestion of a pellet diet, glucose subunits are cleaved and absorbed into the bloodstream.
- β-Cells of the pancreas release insulin, facilitating glucose uptake and its storage as glycogen in the liver and other tissues.
- When blood glucose levels drop, glucagon is secreted from the α-cells of the pancreas to mobilize stored glucose from the liver.
- This interplay between insulin and glucagon helps maintain blood glucose levels within a narrow range despite dietary intake and physical activity.

Alloxan-Diabetic Rats

- The pancreas is compromised with damaged islets of Langerhans, impairing its ability to regulate blood glucose levels effectively.
- Glucose subunits from the pellet diet are not properly cleaved or absorbed.
- The lack of insulin secretion disrupts glucose processing, leading to glucose-starved cells that rely on lipid breakdown for energy.
- Lipid catabolism produces ketone bodies, resulting in acidified blood and potentially causing diabetic ketoacidosis, coma, or death.

2.8 Collection of Blood Samples

Rats were briefly warmed before being anesthetized with chloroform and placed in a container for a short duration. A 1 cm section of the tail was quickly removed using a surgical razor. Blood was collected into EDTA vials for hematological tests and into clean, non-EDTA bottles to allow clotting. Serum was separated from the clot by centrifugation and transferred to clean bottles for biochemical analysis. A cauterizing agent (styptic pencil, silver nitrate) was used to stop the bleeding. When multiple samples were required in a short period, the original wound could be reopened by removing the clot. Additional blood samples could be obtained by removing an extra 3-4 mm of tail (Janet Hoff, 2000).

2.9 Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using the Chi-square test. P-values < 0.01 and 0.05 were considered statistically significant.

3. Results and Discussion

"Diabetes Mellitus represents a group of metabolic syndromes characterized by increased systemic inflammation and oxidative stress, leading to severe complications such as blindness, diabetic foot disease, kidney failure, myocardial infarction, and encephalopathy. Recent research has demonstrated that upregulated inflammation is a primary contributor to metabolic syndrome diabetes. This condition is associated with various factors including insulin resistance, elevated blood lipid levels, ectopic fat deposition, reduced adiponectin levels, increased lipoprotein oxidation, oxidative stress, abnormal mitochondrial function, decreased cellular ATP, altered HDL function, and elevated homocysteine levels" (Akhtar et al., 1981; Shibib et al., 1993).

"Alloxan, a toxic glucose analogue, induces inflammation and generates highly reactive free radicals as by-products of mitochondrial oxidative-reduction reactions (MORR). In healthy cells, these free radicals are neutralized by protective enzymes such as superoxide dismutase (SOD) and catalase. However, in severe diabetic conditions, the activity of these protective enzymes is diminished, leading to damage of macromolecules such as DNA, RNA, and proteins, ultimately causing pancreatic beta-cell dysfunction and death" (Lenzen, 2008).

The acute oral toxicity study of *Momordica charantia* methanolic extract revealed no mortality at doses up to 2500 mg/kg. However, mortality was observed at a dose of 3000 mg/kg in alloxan-induced diabetic rats. Significant increases in fasting blood glucose levels were observed in the diabetic control group compared to the normal control. The methanolic extract of *Momordica charantia* demonstrated hypoglycemic activity on the 10th, 20th, and 30th days of treatment. Notably, the hypoglycemic effect of *Momordica charantia* methanolic extract was found to be more effective than that of Glizid-M (Panacea Biotec) (Table 1, Figure 1).

The extract also significantly reduced serum urea, serum creatinine, and serum cholesterol levels in a dose-dependent manner over 30 days of treatment. Additionally, serum protein levels increased significantly in the extract-treated diabetic rats compared to those treated with Glizid-M (Table 2, Figure 2). The oral glucose tolerance test (OGTT) results showed improved glucose tolerance in diabetic rats treated with *Momordica charantia* methanolic extract, with high doses showing significant hypoglycemic effects after 120 minutes post-glucose load (Table 3, Figure 3).

These findings support the therapeutic potential of *Momordica charantia* in managing blood glucose levels and improving biochemical profiles in diabetic conditions. Akhtar et al. (1981) found that "a dose of 150 mg/kg body weight was effective in alloxan-diabetic rabbits, while lower doses had no effect". Shibib et al. (1993) reported that "the hypoglycemic effects of bitter gourd are attributed to the suppression of gluconeogenic enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase, alongside accelerated glucose metabolism through glucose-6-phosphate dehydrogenase".

This discussion highlights the extract's impact on glucose uptake, consumption, and utilization, its influence on key signalling pathways, and its effects on carbohydrate-digesting enzymes. Additionally, safety considerations including the LD50 (lethal dose for 50% of the population) will be addressed. Research indicates that *Momordica charantia* methanolic extract can significantly enhance glucose uptake and utilization. The extract appears to improve glucose consumption in peripheral tissues, which is crucial for managing blood glucose levels. This effect is likely mediated through its impact on various cellular signalling pathways.

Signalling Pathways: IRS-1/PI3K/Akt: - "One of the primary mechanisms by which *Momordica charantia* exerts its effects is through the activation of the IRS-1 (Insulin Receptor Substrate 1)/PI3K (Phosphoinositide 3-Kinase)/Akt (Protein Kinase B) signalling pathway. This pathway is pivotal in insulin signalling and glucose homeostasis. Activation of IRS-1 leads to the activation of PI3K, which then activates Akt. This cascade enhances glucose uptake by promoting the translocation of glucose transporters (such as GLUT4) to the cell membrane, thereby improving insulin sensitivity and glucose metabolism in tissues" (Khan et al., 2021).

Inhibition of α-Amylase and α-Glucosidase: - "*Momordica charantia* also demonstrates inhibitory effects on α-amylase and α-glucosidase enzymes, which are crucial for carbohydrate digestion and glucose absorption. By inhibiting these enzymes, the extract slows down carbohydrate digestion, leading to a gradual release of glucose into the bloodstream and a reduction in postprandial blood glucose spikes. This action is beneficial in managing diabetes and prediabetes" (Kaur et al., 2020).

Safety and Toxicity: - "Regarding safety, the LD50 of *Momordica charantia* extract has not been extensively documented, but existing studies suggest that the extract is relatively safe when used in moderate amounts. However, high doses could potentially cause gastrointestinal disturbances and other adverse effects. It is important to consider individual variability and pre-existing health conditions when using herbal supplements. Long-term safety data are limited, emphasizing the need for cautious use and further research" (Liu et al., 2018).

4. Conclusions

The methanolic extract of *Momordica charantia* demonstrated greater effectiveness than Glizid-M in reducing circulating blood glucose levels and improving the biochemical profile of diabetic rats. Further studies are needed to explore additional therapeutic potentials of *Momordica charantia*.

Ethical Approval

Animal Ethic committee approval has been collected and preserved by the author(s)

Table-1- Effect of *Momordica charantia* methanolic extract and Glizid –M (Standard drug) on blood glucose level in alloxan induced diabetic albino rats.

Group		Blood glucose levels (mg/dl)		
	0 Day	10th Day	20th day	30th day
Group –A Normal control	90.18±1.07	92.22±6.15	88.62±0.12	87.24±0.66
Group –B Diabetic control	298.10±1.18	310.12±2.12	309.22±3.16	299.14±0.86
Group-C Alloxan +Methanolic Extract (150mg/kg)	295.18±1.77	280.12±2.16	205.22±2.18	190.62±1.8
Group –D Alloxan+Methanolic Extract (300mg/kg)	285.12±1.66	218.02±1.22	195.11±0.17	170.62±0.02
Group –E Alloxan +Methanolic Extract (600mg/kg)	289.16±0.67	210.02±2.67	140.40±3.16	95.85±7.80
Group –F Alloxan+Glizid-M (Standard drug)	285.12±6.45	209.45±3.18	135.18±6.12	110.10±1.18

Values are mean ± SEM, n=8,P<0.05 Vs Diabetic control.

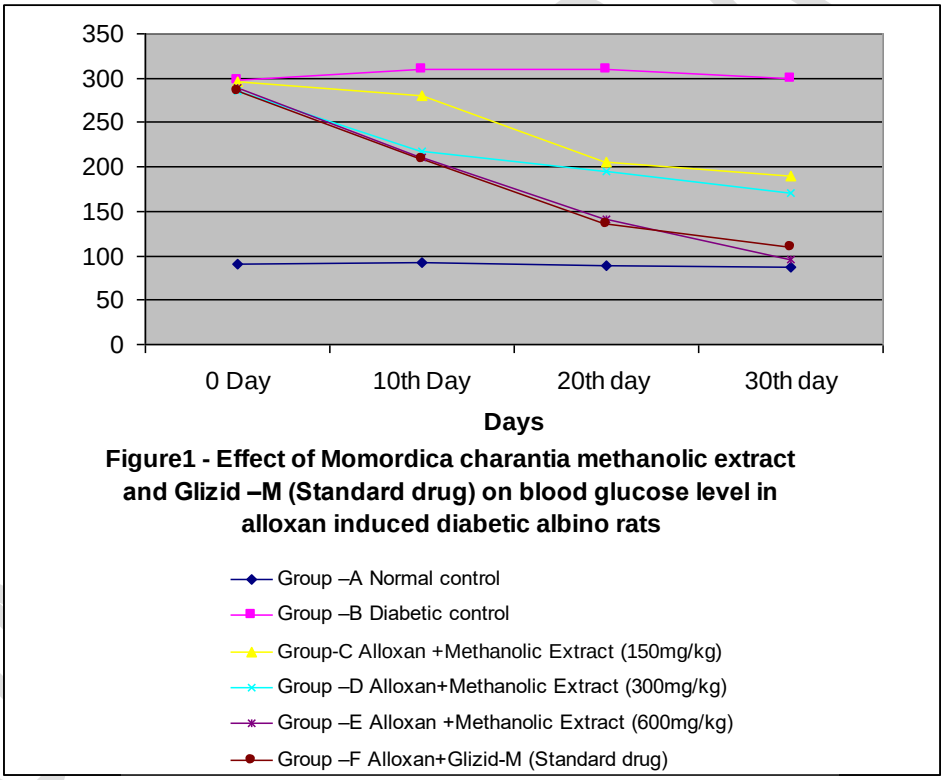

Figure1 - Effect of Momordica charantia methanolic extract and Glizid –M (Standard drug) on blood glucose level in alloxan induced diabetic albino rats

Table-2 Effect of ***Momordica charantia*** methanolic extract on biochemical profile in alloxan induced diabetic rats.

Group Treatment	Serum-Urea (mg/dl)	Serum creatinine (mg/dl)	Serum cholesterol (mg/dl)	Serum protein(mg/dl)
Group A - Normal control	34.01 ± 1.17	0.46 ± 0.09	100.45 ± 1.07	7.18 ± 0.18
Group B - Diabetic control	70.18 ± 2.10	1.58 ± 0.09	205.91 ± 2.46	4.90 ± 0.87
Group C - Alloxan+Methanolic Extract(150mg/kg)	60.20±1.20	1.30±0.7	180.80±2.17	4.71±0.87
Group D - Alloxan+Methanolic extract (300mg/kg)	50.18±1.70**	1.10±0.02**	110.70±4.18**	6.18±0.17**
Group E –Alloxan + Methonolic Extract (600 mg / kg)	30.00±1.80**	0.55±2.7**	105.40±2.07**	8.90±2.17**
Group F - Alloxan+Glizid-M (standard drug)	35.30±1.75***	0.60±2.07***	107.80±2.09***	7.01±2.07***

Values are mean ± SEM, n=8**P<0.001 and ***P<0.05 Vs Diabetic control

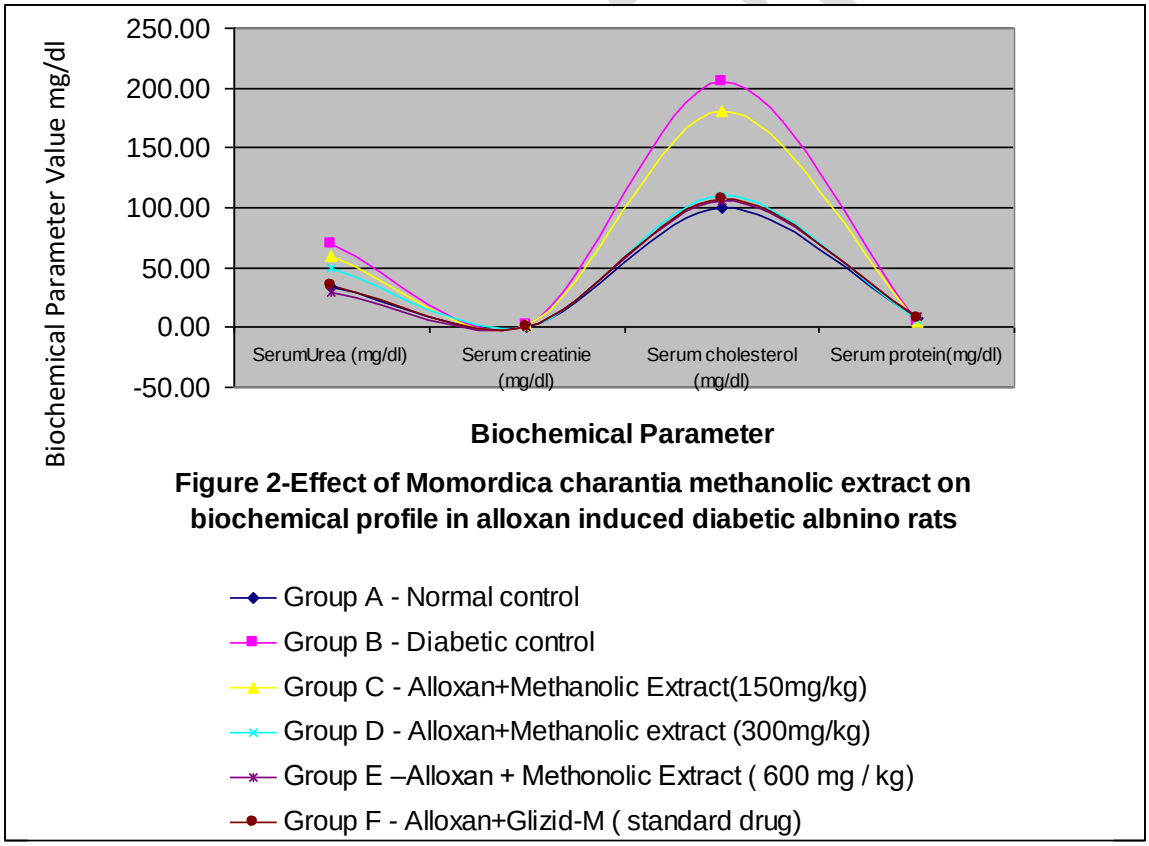

Figure 2-Effect of Momordica charantia methanolic extract on biochemical profile in alloxan induced diabetic albnino rats

Table 3 – Effect of *Momordica charantia* methanolic extract on oral glucose tolerance test in alloxan induced diabetic albino rats.

Blood glucose level (mg/dl)					
Group	0 min	30 min	60 min	90 min	120 min
Group A normal control	90.60±2.60	190.18±4.01	145.09±2.07`	110.20±3.10	95.02±2.09
Group B diabetic control	295.81±7.45	338.8±1.60	370.09±1.2	342.09±9.12	320.20±7.18
Group C alloxan+Methanolic extract (150mg/kg)	120.18±7.42	240.78±7.16	260.60±6.12	205.70±2.60	170.18±4.62
Group C alloxan +Methanolic extract (300mg/kg)	169.12±6.92	220.16±6.12	200.02±5.12	180.18±3.17	160.20±3.28
Group D alloxan+methanolic extract (600mg/kg)	95.02±6.75	210.18±3.14	140.17±3.48	130.18±6.18	95.10±3.28
Group F alloxan +glizid-M (standard drug)	110.02±7.86	240.26±4.12	210.18±1.18	160.18±3.12	110.19±4.29

Values are mean ± SEM, n=8, P<0.05 Vs diabetic control

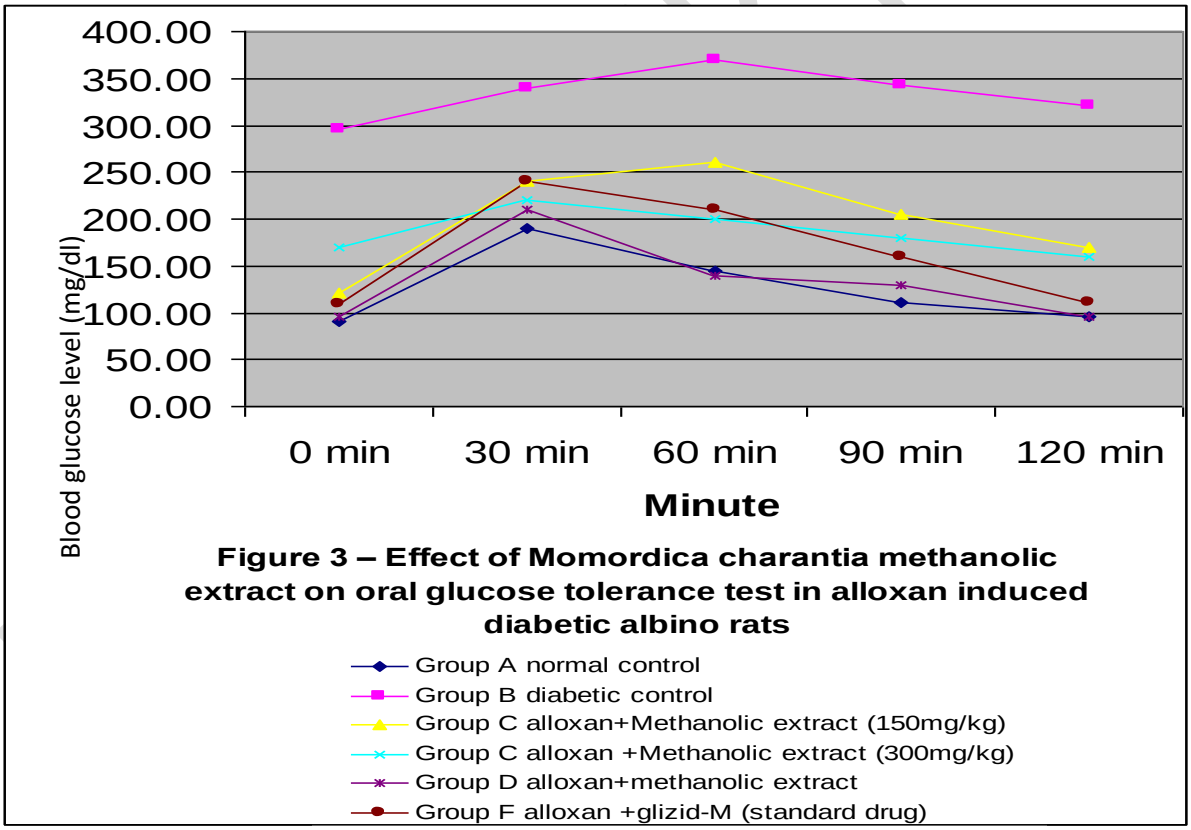

Figure 3 – Effect of Momordica charantia methanolic extract on oral glucose tolerance test in alloxan induced diabetic albino rats

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