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Original Article

Assessment of Antihyperglycemic and Hypolipidemic Activities of Peel Extracts of *Annona squamosa, Actinidia deliciosa* and Other Two Fruits in Alloxan-induced Diabetic Rats

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ABSTRACT

Objectives: This study aims to assess the potential antidiabetic properties of aqueous extracts derived from the peels of specific fruits, including *A.squamosa, C. melo, A. deliciosa* and *M. pumila*. **Materials and Methods:** Male rats of the Wistar albino strain, weighing 180-200 g, were divided into 12 groups, with one group as the control. Diabetes was induced using alloxan, followed by treatment with fruit peel extracts and a polyherbal mixture. After a 28-day experimental window, the rats were euthanized and specimen pancreatic tissues and blood samples were analyzed. **Results:** The findings indicated that blood glucose concentrations were substantially reduced by all selected extracts and the polyherbal mixture. Moreover, they demonstrated positive effects on serum lipid profiles, decreasing triglycerides, total cholesterol, LDL and VLDL, while increasing HDL levels and insulin concentrations. Notably, the polyherbal mixture and *M. pumila* (apple) peel extract exhibited robust anti-diabetic effects, even at lower doses, surpassing the other three extracts. Results were correlated strongly with histopathological analysis of pancreatic tissue. **Conclusion:** This study highlights the considerable therapeutic potential of selected extracts of the fruit peels and their mixture in diabetes management. Their ability to mitigate pancreatic damage positions them as promising candidates for the development of potent antidiabetic agents.

Keywords: Fruit peels, Alloxan, Hyperglycemia, Hypolipidemia, Polyherbal mixture.

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INTRODUCTION

Diabetes Mellitus (DM) is a common non-communicable disease characterised by extreme resistance to insulin, giving rise to oxidative stress.[1] Hyperglycemia arises from disrupted glucose metabolism due to insufficient insulin, leading to oxidative stress and heightened lipid peroxidation. These factors contribute to the development of secondary complications associated with diabetes. Diabetes is a growing epidemic and a major health concern, ranking third after cancer and cerebrovascular diseases.[2]

In 2015, approximately 415 million people had DM, with a projected rise to 642 million by 2040 in emerging economies.[3] The economic impact of Diabetes Mellitus (DM) is significant, with an approximate expenditure of $673 billion in 2015, constituting 12% of the global health budget for that period. While diabetes is acknowledged as a public health concern primarily in urban regions of emerging economies, recent information reveals a growing prevalence of diabetes in rural areas as well.[4] In 2015, India recorded 69.1 million individuals affected by DM, positioning it with the second-highest number of diabetes cases globally, after China.

DM-specific complications include retinopathy; nephropathy and neuropathy, causing substantial morbidity among patients with both type I and type II Diabetes Mellitus.[5] Conventional treatments for diabetes primarily involve lifestyle management and oral hypoglycemic medications, focusing on glucose level regulation rather than disease reversal. This underscores the continued quest for effective diabetes treatments.[6]

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Extensive evidence suggests that the creation of oxygen-free radicals and oxidative radical stress plays a pivotal role in diabetic implications. Several biochemical pathways closely linked to hyperglycemia contribute to increased free radical production, for instance, glucose autoxidation, the sorbitol aldose reductase pathway, prostaglandins synthesis and Maillard reaction.[7]

Despite a wide array of available antidiabetic medications, the search for safer and more cost-effective alternatives persists. This highlights the potential of antioxidant-rich medicinal plants as substitutes for existing antidiabetic drugs. Lately, there has been a growing emphasis on investigating the antioxidant capabilities of phytochemicals in common dietary sources, especially fruits and vegetables. Significantly, numerous studies have established that several of these phytochemicals, known for their antioxidant capabilities, are predominantly concentrated in peels. Regrettably, the outer parts (peels) of fruits as well as vegetables are frequently disposed of, contributing to environmental waste. However, in recent years, researchers have increasingly recognized the value of these peels, extracting bioactive compounds with a range of health benefits, including antioxidative, anti-inflammatory, anticancer, antiviral and cardioprotective properties.[8]

Numerous studies have confirmed that fruit and vegetable peels are rich in phenolic compounds, with higher concentrations in the peels than in the pulp.[9,10] For instance, *Malus pumila* (apple), a widely recognized and consumed fruit, is esteemed for its various health benefits. The peels of apples, specifically, have been demonstrated to contain a high concentration of polyphenols and showcase antioxidant as well as antiproliferative properties.[11]

A.squamosa, commonly referred to as custard apple, is a small tree belonging to the Annonacea family. Traditionally, diverse components of *A. squamosa*, encompassing its barks, leaves, seeds and fruits were used for the traditional treatment of various health conditions.[12] Studies have revealed antimicrobial and antioxidant activities in *A.squamosa* peels.[13]

A.deliciosa (kiwi), commonly known as kiwi, is a globally recognized fruit, with its fruits known for their unique taste and medicinal properties. This fruit is rich in phytoconstituents such as triterpenoids, flavonoids, phenylpropranoids, quinines and steroids. Within traditional Chinese medicine, diverse elements of *A. deliciosa* are employed for addressing a range of ailments such as like liver disorders, bleeding gums, inflammation, rheumatoid arthritis and different types of malignancies.[14] Substantiated by scientific findings, *A. deliciosa* fruit peel's antioxidant, antimicrobial and antitumor properties were well-established.[15]

C. melo Linn, also known as musk melon, belongs to the Cucurbitaceae family. Different components of this plant, including the pulp, roots, seeds and seed oil, have been historically utilized as an astringent, emmeno- and galacto-gogue, diuretic, coolant, emmolient, aphrodisiac. Throughout history, the fruit has been employed to address kidney disorders, bladder stones, urinary tract problems, as well as diverse conditions like liver and biliary disorders.[16] Previous investigations have indicated good antioxidant activity in the skin of *C. melo* (musk melon).[17]

Given these considerations, the primary goal of our research is to explore the therapeutic potential of the peels from these four different fruits and their Polyherbal mixture (PHF).

MATERIALS AND METHODS

Plant Material Collection

Fresh fruits were acquired from the local market and peels were removed after thoroughly washing under tap water.

Preparation of Peel Extracts and PHF (Polyherbal Mixture)

To prepare the peel extracts and the Polyherbal Mixture (PHF), the peels were meticulously dried in the shade. Subsequently, they were finely ground using a blender. Every sample was meticulously weighed and cold maceration was employed for extraction using a mixture of water (80 parts) and ethanol (20 parts) for duration of 72 hours. Following this period, the samples underwent filtration and concentration. The resultant extracts were converted into comminuted form and preserved for future usage. Selected fruit peel extracts were blended in accurate proportions (1:1:1:1 ratio) to get a polyherbal mix.

Phytochemical Screening

The aqueous extracts of peels underwent an extensive phytochemical examination using established screening techniques.

Experimental Subjects

Male Albino Wistar rats, with weights ranging from 180-200 g, were sourced from Mahaveer Laboratories in Hyderabad, Andhra Pradesh, India. These rats are kept in a controlled environment with a temperature set at 23±1^{o}C, a relative humidity of 50±10% and a 12:12 light-dark cycle. They had unrestricted access to both water and a standard laboratory diet consisting of lipids (5%), protein (25%) and carbohydrates (75%) procured from Unilever HUL, Bengaluru. A two-week acclimatization period was observed before the initiation of the experiment. All aspects of animal housing, handling and experimental procedures strictly adhered to the guidelines established by the IAEC (Registration No. 516/01/A/CPSCEA).

Acute Toxicity Test

In accordance with OECD guidelines (423), acute toxicity tests were conducted on the aqueous extract. Wistar albino rats, weighing between 150-200 g, were divided into 10 groups, each comprising six animals. These groups were subjected to varying doses of the extract, ranging from a minimum of 200mg/kg to a maximum of 2000 mg/kg, administered orally. The rats were closely monitored for any signs of abnormalities, toxic reactions, or mortality.

Hyperglycemia Induction

Hyperglycemia was induced in male Wistar albino rats weighing 180-220 g by enforcing overnight fasting (12-14 hr). Prior to inducing hyperglycemia, their body weight and fasting BG levels were measured using a glucose meter. A single intraperitoneal injection of freshly prepared alloxan monohydrate solution (20 mg/kg body weight) was administered to induce hyperglycemia. The alloxan solution, tailored to the weight of each animal, was dissolved in 0.5 mL of sodium citrate at a pH of 4.5 before being administered through injection. Subsequently, after giving alloxan, fodder and water be available to the animals, 30 min later.

Experimental Protocol

Following the induction of diabetes, rats with BG levels surpassing 350 mg/dL were chosen for participation in the research. These chosen animals were then categorized into groups based on their respective body weights. Over a 14-day period, the animals received oral administration of standard gliclazide and the chosen peel extracts. Various parameters were evaluated at the end of the 14-day study. At the end of the 14th day, blood sampling was done on all animals under mild ether anaesthesia by puncturing retro orbital plexus. Subsequently, the animals were euthanized and hepatic tissues were excised for further analysis.

The rats were alienated into groups, each involving six rats.

Top of Form

Group 1: Control group without any intervention.

Group 2: Alloxan treated disease control group.

Group 3: Gliclazide (1mg/kg) treated Standard group.

Group 4: Alloxan-induced group receiving 200 mg/kg of aqueous peel extract from *A. squamosa.*

Group 5: Alloxan-induced group receiving 400 mg/kg of aqueous peel extract from *A. squamosa.*

Group 6: Alloxan-induced group receiving 200 mg/kg of aqueous peel extract from *A. deliciosa.*

Group 7: Alloxan-induced group receiving 400 mg/kg of aqueous peel extract from *A. deliciosa.*

Group 8: Alloxan-induced group receiving 200 mg/kg of aqueous peel extract from *C. melo*. Group 9: Alloxan-induced group receiving 400 mg/kg of aqueous peel extract from *C. melo*. Group 10: Alloxan-induced group receiving 200 mg/kg of aqueous peel extract from *M. pumila.*

Group 11: Alloxan-induced group receiving 400 mg/kg of aqueous peel extract from *M. pumila.*

Group 12: Alloxan-induced group receiving 200 mg/kg of a Polyherbal Formulation (PHF).

Estimation of Biochemical Parameters

Biochemical parameter assessment involved subjecting blood samples to centrifugation for at least 10 min at a speed of 3000 rpm in order to isolate the serum. The collected samples of serum were then utilized to determine various parameters, including BG, HbA1c, insulin levels and the serum lipid profile, which included TG, TC, HDL, LDL and VLDL. These assessments were carried out on all animals after a 28-day study period. The methodologies adhered to the standard procedures established by the IFCC and all measurements were conducted employing commercial diagnostic kits.

Histopathological Studies

In the histopathological analysis, the pancreas was meticulously removed and washed with ice-cold normal saline. Simultaneously, a segment of the liver excised from any animal from every group was immersed in formalin (10%) and was selected for subsequent histopathological scrutiny. The gathered pancreatic tissues underwent processing and embedding in paraffin wax. Sections with a thickness of approximately 5-6 μm were generated and subjected to staining with hematoxylin and eosin dye. Subsequent to staining, a microscopic examination of these sections was carried out to identify any histopathological alterations.[20-22]

Statistical Analysis

The statistical evaluation of the data derived from the biochemical parameters encompassed the presentation of mean values along with the Standard Error of the Mean (SEM). Statistical analyses were executed through ANOVA, pursued by DUNNETT's test. The study defined a significance threshold at $p \leq 0.05$.

RESULTS

The effectiveness of peel extracts derived from specific fruits such as *A. squamosa, A. deliciosa, C. melo* and *M. pumila* was assessed in diabetic rats induced with alloxan. These peel extracts displayed significant decreases in overall blood glucose, glycosylated hemoglobin and total cholesterol levels. Additionally, they demonstrated elevated insulin and triglyceride levels, effectively regulating levels of the lipids.

Preliminary Phytochemical Analysis

The aqueous peel extract of *A. squamosa* revealed polyphenols, carbohydrates, glycosides, alkaloids and terpenoids *A. deliciosa*'s aqueous fraction contained phenols, triterpenoids and steroid compounds. The aqueous fraction from *C. melo* exhibited the existence of flavonoids, sapogenins, carbohydrates, polyphenols and steroid compounds. Regarding *M. pumila*, the phytochemical assessment of the aqueous extract indicated the occurence of flavonoids and other glycosides, terpenoids and steroid compounds (Table 1).

Acute Toxicity

The rats administered with the peel extracts exhibited no signs of toxicity and there were no fatalities even at the highest dose of 2000 mg/kg. Consequently, for the pharmacological investigations, we chose dosages at $1/5^{th}$ and $1/10^{th}$ of the maximum dose (2000 mg/kg).

Effect of Aqueous Peel Extracts on the levels of BG, Insulin and HbA1c

Table 2 and Figures 1-3 illustrate the impact of chosen extracts and the Polyherbal mixture (PHF) on serum insulin, BG and HbA_{1c} levels. In comparison to Group 1, Group 2 demonstrated a significant elevation in blood glucose and glycosylated haemoglobin levels. Conversely, Groups 3-12 exhibited a noteworthy reduction ($p<0.05$) in blood glucose and glycosylated haemoglobin levels, bringing them closer to normal levels. Serum insulin levels in the disease control rats were markedly lower than those in the control group (Group 1). However, Groups 3-12 showed increased serum insulin levels while put side by side to the Group 2 (disease control).

The Influence of Chosen Peel Extracts on Lipid Panel Levels

The impact of chosen extracts and a polyherbal mixture on complete lipid panel levels is detailed in Table 3 and illustrated in Figures 4-8. In comparison to the control group (Group 1), the disease control group (Group 2) showed heightened TC and TG levels, which were mitigated in groups receiving peel extracts in treatment groups. Furthermore, the levels of LDL and VLDL were significantly lower in the groups receiving peel extracts (treatment groups) compared to the disease control (Group 1). Groups administered with peel extracts (Group 3-12) displayed notably increased HDL levels in contrast to the disease control group (Group 1).

Table 1: Initial Phytochemical Assessment of Aqueous Extracts from Chosen Fruit Peel.

Fruit	Phytochemicals
A. squamosa	Alkaloids, Phenolic Comp, Saponins, Triterpenes, Carbohydrates, Tannins.
A. deliciosa	Phenolic Comp, Triterpenes, Steroids.
B. melo	Flavonoids, Saponins, Carbohydrates, Steroids, Tannins.
M. pumila	Glycosides, Flavonoids, Terpenoids, Steroids.

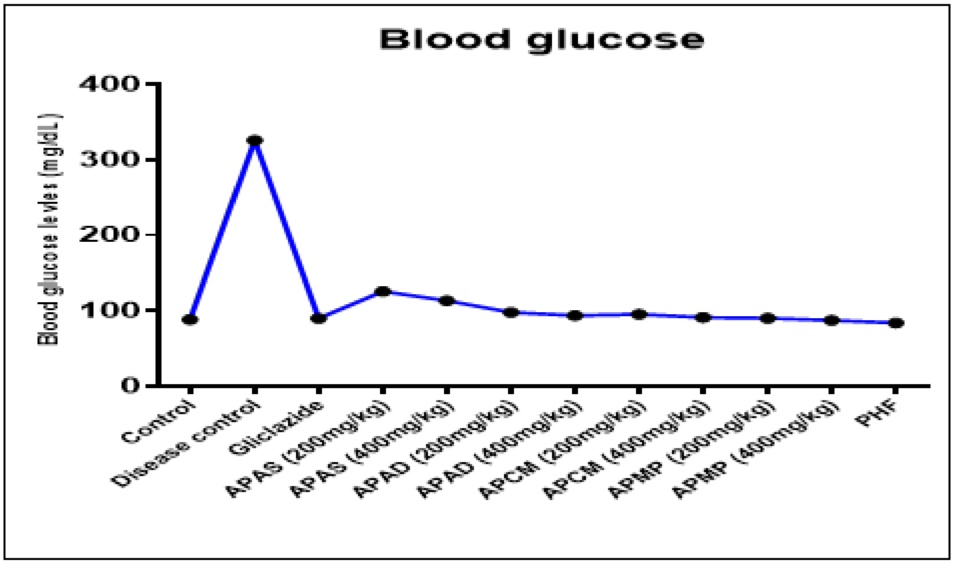

Figure 1: Impact of Chosen Extracts and PHF on BG Levels.

Table 2: Effects of chosen plant extracts and PHF on BG, HbA_{1c} and insulin levels in diabetic rats.

Groups	Blood Glucose (mg/dL) (Mean±SEM)	Glycosylated Haemoglobin (%) (Mean±SEM)	Insulin (µIU/mL) (Mean±SEM)
Control	88.66±3.39	4.41±0.23	8.34±0.12
Disease Control	326.00±6.65	10.96±0.23	4.41±0.20
Gliclazide	90.16±2.52*	4.72±0.11*	8.71±0.19*
APAS (200 mg/kg)	125.83±3.28$	7.23±0.14*	7.21±0.14*
APAS (400 mg/kg)	113.66±4.27$	6.30± 0.15*	8.05±0.06*
APAD (200 mg/kg)	98.00±3.74$	5.92±0.10*	7.84±0.13*
APAD (400 mg/kg)	93.83±2.53*	5.88±0.23*	8.37±0.08*
APCM (200 mg/kg)	95.50±2.61*	5.84±0.16*	8.04±0.15*
APCM (400 mg/kg)	91.33±2.02*	5.76±0.22*	8.33±0.10*
APMP (200 mg/kg)	90.33±2.95*	5.20±0.13*	7.97±0.13*
APMP (400 mg/kg)	87.66±2.81$	4.72±0.17*	8.46±0.12*
PHF	84.00±1.87*	4.36±0.12*	8.67±0.10*

$p>0.05$ ns, $p<0.001$*, $p<0.01$#, $p<0.05$ $ one way ANOVA followed by DUNNETT's multiple comparison test. $n=6$ all groups were compared with standard group.

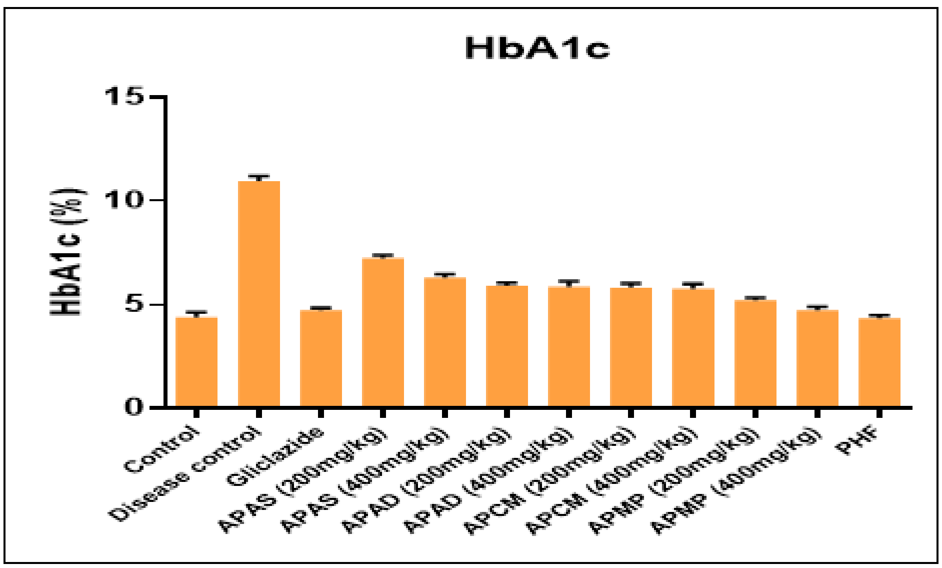

Figure 2: Influence of Selected Extracts and PHF on HbA_{1c} Levels.

Investigation of Pancreatic Histopathology Following Treatment with Selected Peel Extracts

Figure 9 presents the histopathological assessment of the pancreas across various groups, including 1, 2, 3, 5, 7, 9, 11 and 12. Group 1, consisting of normal rats, showcased a healthy pancreas characterized by compact acini with connective septa and distinct Islets of Langerhans within the exocrine tissue.

Contrastingly, pancreatic tissues in Alloxan-induced diabetic rats (Group 2) revealed evident damage, densely packed acini and a reduced cell count. Distinct cellular infiltrates were noticeable surrounding specific capillaries, ducts and acini of the pancreas.

Upon examining the pancreatic tissues of hyperglycemic rats given Gliclazide (Group 3), findings made known closely packed clusters of cells in the pancreas responsible for enzyme production and expanded ducts lined with flattened epithelial cells.

Significantly, there was an observable reduction in the infiltration of cells around the dilated ducts and certain clusters of pancreatic cells (acini).

Samples from the pancreas of animals treated with *A. squamosa* peel extract at 400 mg/kg (Group 5) demonstrated improvement in damage and necrosis in the pancreatic duct and islets. Similarly, *A. deliciosa* peel extract at 400 mg/kg (Group 7) shows the

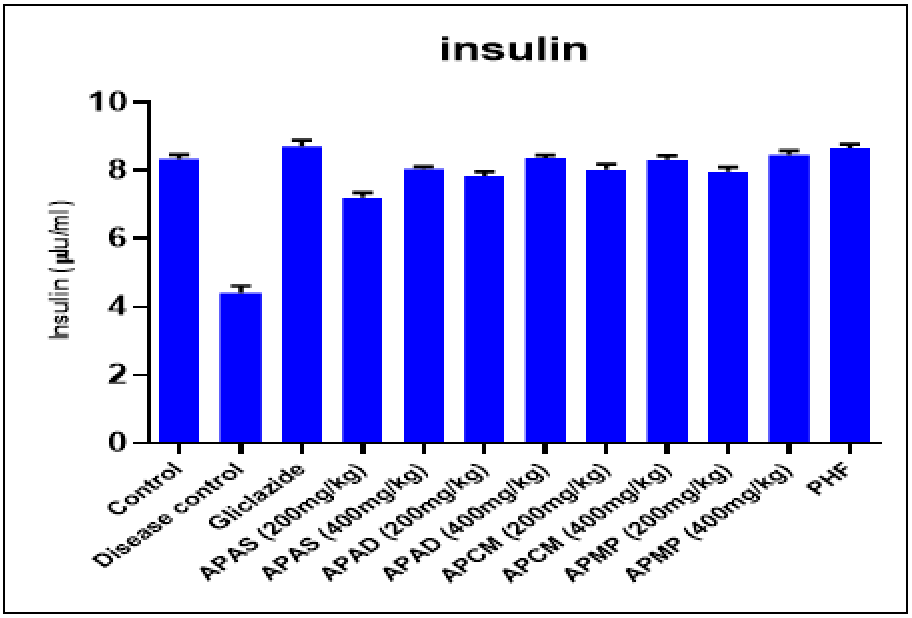

Figure 3: Effects of Selected Extracts and PHF on Insulin Levels.

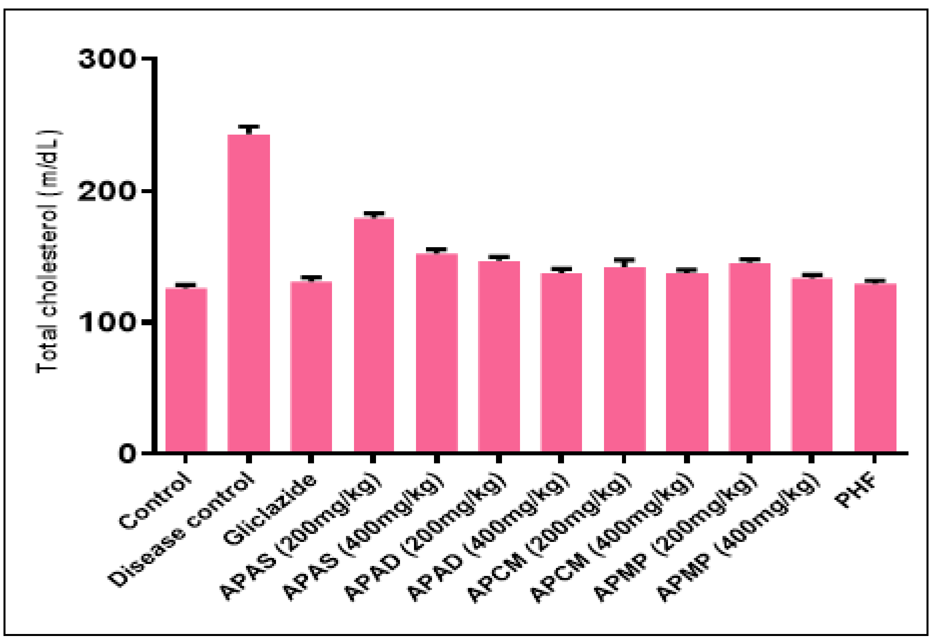

Figure 4: Impact of Selected Extracts and PHF on TC Levels.

incidence of Langerhans islet which are pale and oval in shape, closely packed clusters of pancreatic cells (acini) and infiltration of cells.

In the case of *C. melo* peel extract at 400 mg/kg (Group 9), collagen fibers were visibly identified round the specific blood capillaries and ducts of pancreas. Treatment with *M. pumila* peel extract at 400 mg/kg (Group 11) led to a significant recovery of tubules with densely packed clusters of pancreatic cells (acini) and an islet of Langerhans exhibited an improved arrangement of exocrine tissue, along with evident dilation of blood vessels.

The Polyherbal Formulation (PHF) treatment group (Group 12) exhibited well-defined pancreatic islets, pancreatic ducts and tightly packed clusters of cells in the pancreas (acini).

Table 3: Impact of Selected Extracts and PHF on Lipid Panel Levels.

Groups	Total Cholesterol (mg/dL) Mean±SEM	Triglycerides (mg/dL) Mean±SEM	HDL (mg/dL) Mean±SEM	LDL (mg/dL) Mean±SEM	VLDL (mg/dL) Mean±SEM
Control	126.00±2.74	81.16±2.65	62.29±0.96	47.43±2.12	16.26±1.21
Disease Control	243.16±5.62	132.00±2.50	34.05±0.24	182.71±5.95	26.41±0.87
Gliclazide	131.33±3.01$	82.33±2.30$	57.09±0.82$	57.77±3.25$	16.46±0.23*
APAS (200 mg/kg)	179.50±3.47$	109.66±3.49$	45.83±0.96#	111.73±3.08$	21.93±0.06ns
APAS (400 mg/kg)	152.33 3.45$	95.83±3.57$	45.68±0.44$	79.85±2.58$	19.16±0.09*
APAD (200 mg/kg)	147.00±2.90$	103.00±2.51$	56.39±0.72$	80.72±2.67$	20.62±0.07 ns
APAD (400 mg/kg)	137.66±3.14$	89.50±1.83$	56.05±0.56$	63.28±3.24$	17.93±0.12*
APCM (200 mg/kg)	142.00±5.56$	100.66±2.30$	52.05±0.57$	69.21±2.41$	20.13±0.24*
APCM (400 mg/kg)	137.50±2.39$	87.83±2.85$	54.24±0.14$	67.27±2.12$	17.56±0.42*
APMP (200 mg/kg)	145.66±2.44$	98.83±2.08$	52.85±0.34$	70.32±1.67$	19.76±0.51*
APMP (400 mg/kg)	133.66±2.70$	85.66±1.96$	60.21±0.73$	56.32±3.54$	17.13±0.42*
PHF	129.33±2.60$	80.66±2.87$	62.12±0.94$	51.03±2.32$	16.13±0.84*

$p>0.05$ ns, $p<0.001$*, $p<0.01$#, $p<0.05$ $ one way ANOVA followed by DUNNETT's multiple comparison test. $n=6$ all groups were compared with standard group.

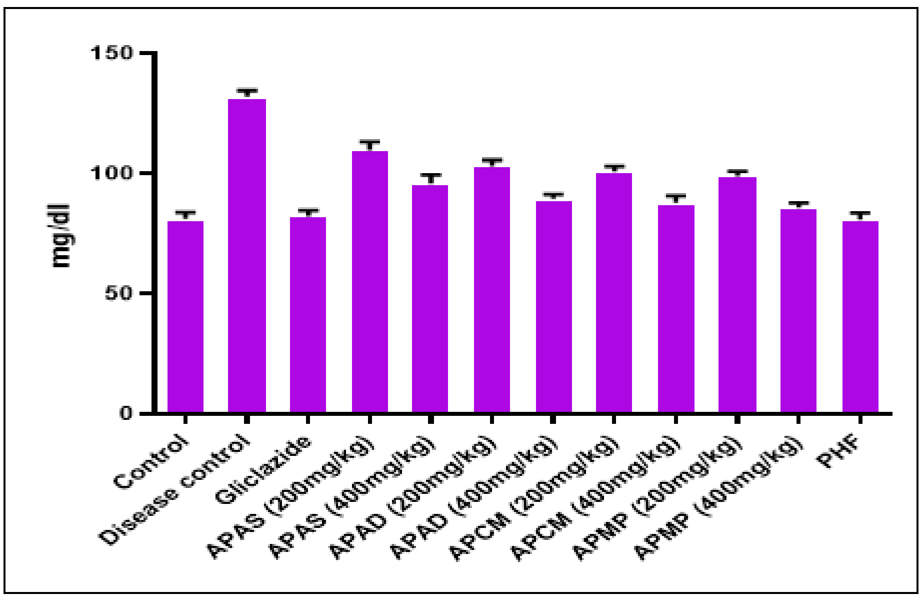

Figure 5: Influence of Selected Extracts and PHF on TG Levels.

DISCUSSION

Inducing hyperglycemia through Alloxan administration, whether through parenteral, intravenous, intraperitoneal, or subcutaneous routes, is a well-established method for inducing diabetes in animal models. The induction of diabetes in this context arises from the swift absorption of Alloxan by pancreatic β cells, causing their sudden destruction. Alloxan induction triggers oxidative stress and the generation of reactive oxygen species in the pancreas. While a similar uptake occurs in the liver, other tissues exhibit greater resistance to reactive oxygen species than pancreatic β cells, providing a protective mechanism against Alloxan-induced toxicity.

This study had a specific focus on assessing the potential antidiabetic effects of extracts derived from fruits: *A. squamosa, A. deliciosa, C. melo* and *M. pumila*. The induction of diabetes using alloxan led to an elevation in blood glucose levels attributed to oxidative stress; however, the administration of the chosen peel extracts and the Polyherbal Formulation (PHF) significantly alleviated these heightened BG levels. The sequence of efficacy among the extracts of peel was determined as APAS<APAD<APCM< APMP<PHF, based on their

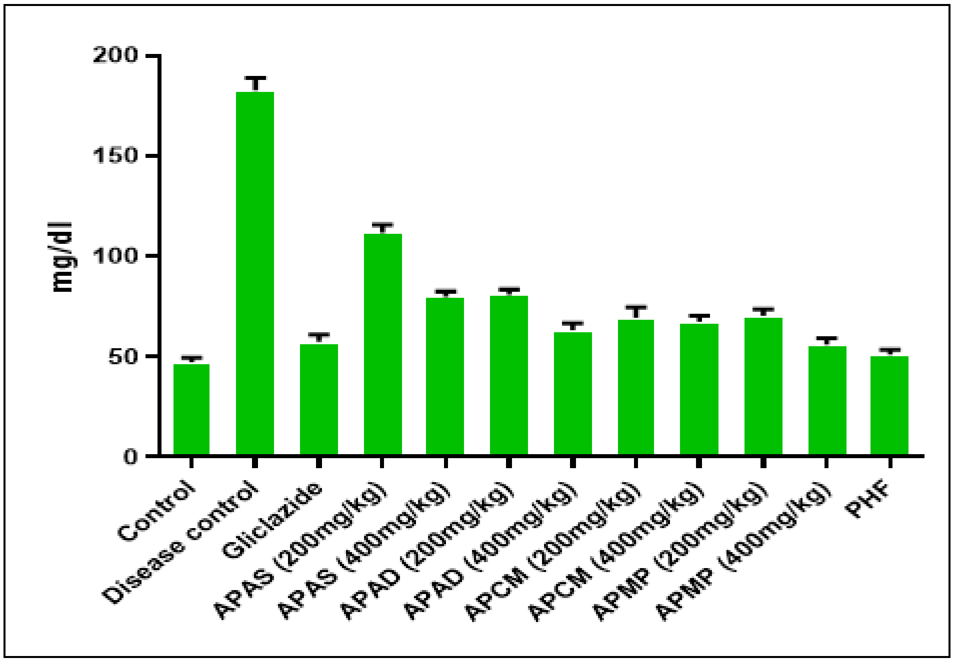

Figure 6: Effect of Selected Extracts and PHF on LDL Levels.

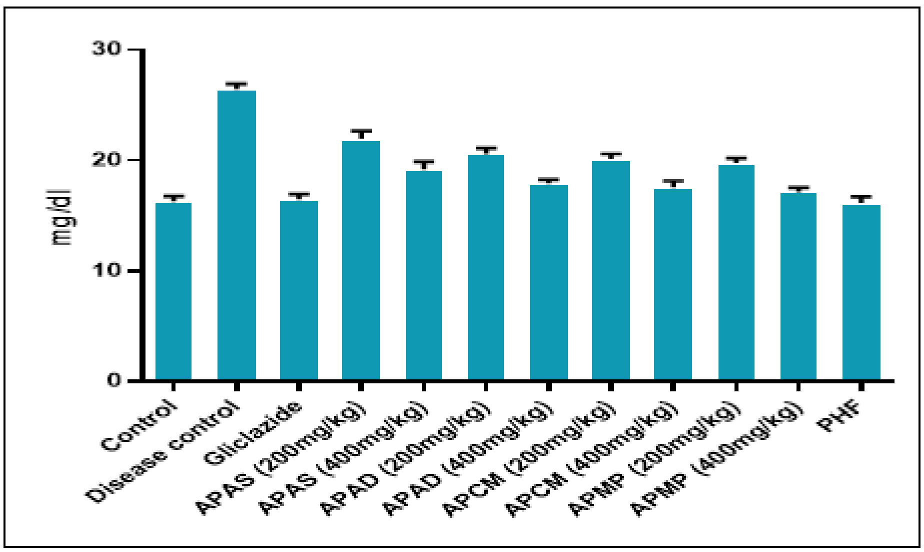

Figure 7: Impact of Selected Extracts and PHF on LDL Levels.

demonstrated hypoglycemic activity in diabetic rats. All selected plant peel extracts and the PHF consistently induced a reduction in blood glucose levels, contributing to a decline in glycosylated hemoglobin levels.

Furthermore, therapy with these peels extracts reduced elevated serum lipid levels, including triglycerides and total cholesterol, while increasing High-Density Lipoprotein (HDL) levels. Histopathological analysis revealed that the peel extracts ameliorated pancreatic damage, restoring normal pancreatic structure with closed and packed acini and visible islets of Langerhans within the exocrine tissue.

In contrast, diabetic rats exhibited injured pancreas with densely packed acini and reduced cell numbers. Gliclazide treatment led to closely packed pancreatic acini and dilated ducts with flat epithelial linings, with reductions in cellular infiltration. Individual peel extract treatments showed varying degrees of amelioration, including damage and necrosis reduction, the presence of Langerhans islets, observable collagen fibers and improved exocrine tissue arrangement. The polyherbal formulation demonstrated well-defined pancreatic islets, ducts and tightly packed acini.

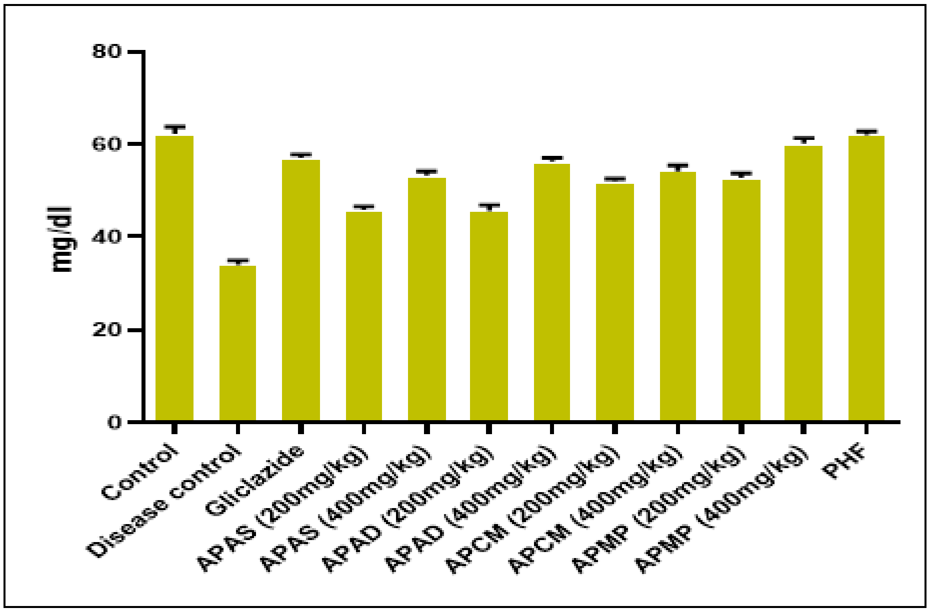

Figure 8: Influence of Selected Extracts and PHF on HDL Levels.

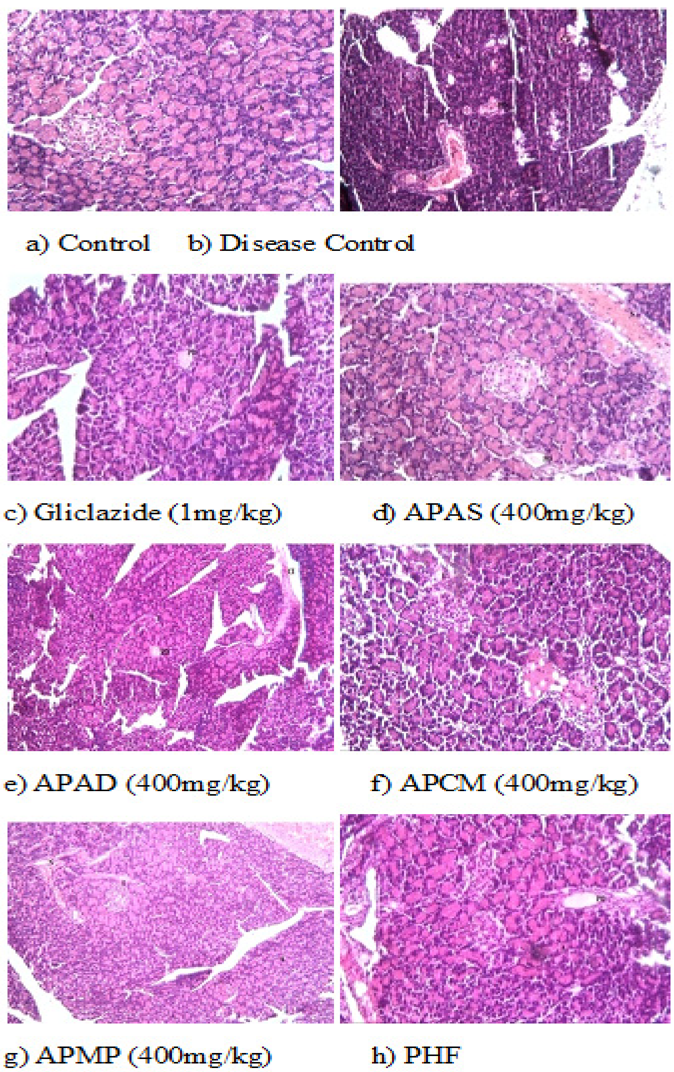

Figure 9: Histopathology of Pancreas (45X).

CONCLUSION

In conclusion, this study underscores the notable antihyperglycemic and hypolipidemic actions of chosen extracts in diabetic rats. These effects are likely due to the presence of diverse phytochemicals in the peel extracts. The polyherbal mixture exhibited more significant effects than individual peel extracts. Further investigations are needed to elucidate underlying mechanisms and establish the potential of polyherbal mixtures as nutraceuticals and dietary supplements for individuals with diabetes.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ABBREVIATIONS

APAS: *A. squmosa* Aqueous peel extract; **APAD:** *A. deliciosa* Aqueous peel extract; **APCM:** *C. melo* Aqueous peel extract; **APMP:** *M. pumila* Aqueous peel extract; **PHF:** Poly Herbal Mixture; **BG:** Blood Glucose; **HbA$_{1c}$:** Glycosylated Haemoglobin; **TG:** Triglycerides; **TC:** Total Cholesterol; **HDL:** High Density Lipoproteins; **LDL:** Low Density Lipoproteins; **VLDL:** Very Low Density Lipoproteins; **IACE:** Institutional Animal Ethics Committee; **IFCC:** International Federation of Clinical Chemistry; **ANOVA:** Analysis of Variance; ***A. squmosa*:** *Annona* *squamosa;* ***A. deliciosa*****:** *Actinidia deliciosa*; ***C. melo*****:** *Cucumis melo;* ***M. pumila*****:** *Malus pumila.*

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