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Original Article

Effects of *Carica Papaya* and *Psidium Guajava* Extracts on Hepato-Renal Performance of Streptozotocin-Induced Diabetic Male Albino Rats

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Abstract

The growing number of diabetes coupled with the harsh side effects of some synthetic drugs has led to the increasing search for alternative medicine which are relatively cheap with minimum side effects. **Objective:** To investigate the anti-diabetic effect of ethanolic extract of *Carica papaya* and *Psidium guajava* extracts separately and in combination, and the effect of treatment on hepato-renal performance. **Methods:** Papaya and guava leaves were macerated in 98% ethanol for extraction. **Results:** The result showed that ethanolic leaf extract of *P. guajava* and *C. papaya* significantly ($P< 0.05$) reduced blood glucose level, Total Cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and significant increase in high density lipoprotein (HDL) as compared to diabetic control group. Serum activities of liver enzymes such as aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) was slightly elevated that indicate hepatotoxic nature of plant extracts. The level of gamma-glutamyl transferase (GGT), bilirubin and HbA1C level were restored to normal range. A slight reduction in body weight ($P>0.05$) of treated groups was observed. Serum urea and creatinine concentration was restored to normal level in treated rats with regeneration of kidney function. **Conclusions:** The study concluded that individual and combined plant extract show anti-hyperglycemic effect but the combined remedy at this dose show hepatotoxicity.

Keywords: *Carica papaya*, *Psidium guajava*, streptozotocin, ethanolic extract, anti-hypergylcemic

Introduction:

Diabetes mellitus is one of the common metabolic disorders of human beings. The identifying feature of diabetes is persistent elevated blood glucose level resulted from deficiency in regulation or secretion of insulin hormone. The abnormality in insulin secretion also leads to disturbance in carbohydrates, protein and fat homeostasis. The propagation of diabetes is increasing in developing nations as well as middle-income countries [1].

Diabetes is related with multiple manifestation in which predominately is high blood glucose level. The deleterious effects associated with diabetes are hyperglycemia, hyperlipidemia, hypertension, blindness, limb amputation and failure of liver, kidneys and nervous system. The endocrine imbalance puts patients at the verge of micro and macro-vascular diseases that is main cause of morbidity and mortality [2].

Liver and kidneys are vital organs of the body to regulate metabolism. It was reported by previous investigations that liver is main organ affected by diabetes. In United States, the drug induced liver injury is more common cause of liver failure. Almost 10% of the diabetic patient with hepatotoxicity will die or required

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immediate liver transplant to reduce drug-induced liver injury [3]. Diabetic nephropathy is a serious complication of diabetes. With the increase in diabetes prevalence a sharp rise in kidney failure has been observed. Approximately 20-40% of diabetic patients having type 1 and Type 2 develop nephropathy [4].

Over few decades the demand of herbal drugs has increased globally due its remedial effects and safety. Herbal drugs are preferred over synthetic because of its less toxicity and cost effectiveness. According to World health organization 80% of the world population relies on plants as an exclusive source of drugs [5]. Plants are enriched with phytochemicals that are key for therapeutic and drug development. According to estimation there are 25,000 higher plants in which 2500 species are investigated with pharmacological effects against diabetes mellitus [6].

Carica papaya is a perennial, herbaceous plant remains an important source of food and medicine for humans. The nutritive value of papaya plant is accepted worldwide due to its multidimensional therapeutic effects. The leaves of papaya are very helpful for treatment of malaria, dengue, jaundice, immunomodulatory and viral diseases. *Psidium guajava* is well known medicinal plant grown in tropical and subtropical areas. The plant is broadly used in medicine all over the world. The medicinal properties of guava leaves are shown by many investigations [7]. The leaves of guava are used as traditional medicine in Asian countries and all over the world for the management of diabetes mellitus, cancer and heart diseases. The guava leaf infusion which is readily available in every household along with rice powder is effective therapy against cholera related death [8].

The present study was conducted to explore the potential of *C. papaya* and *P. guajava* extracts for diabetes that might control the glucose level of rats and exert positive effects on the health parameters of streptozotocin-induced diabetic rats.

Methods:

Collection of Plant Leaves

Fresh, green, healthy leaves of *C. papaya* and *P. guajava* were collected from a Local area in the month of June. Afterwards the processed leaves were stored at room temperature for further use.

Preparation of Plant Extract

The dried leaves of *P. guajava* and *C. papaya* were stocked at room temperature for the preparation of extract. The leaves were pulverized to get fine powder using an electric grinder. The extraction was carried out in ethanol. For extraction, about 250 g of powdered *P. guajava* and *C. papaya* leaves were saturated in 10mg/100 ml of ethanol (98%) in different conical flask. The solution were mixed thoroughly and allowed to stand at room temperature for 72 hours. The regular stirring was performed to dissolve the mixture completely. After three days, the resulting mixture was filtered through whatman filter paper No. 1. The left over residue was filtered through muslin cloth. The liquid filtrates were condensed and evaporated to dryness at 40°C using rotary evaporator. The evaporated filtrates were poured in large size Petri plates and allowed to dryness overnight. It produced green color, solid residue of guava and papaya that was collected by spatula. The extracts yield was calculated. The dried residues of both plants were poured in glass vials and stored in refrigerator at 4°C for further use. From this stock, the fresh dose of animals was prepared whenever it was required.

Dose Calculation and Preparation

Dose prepared according to the body weight of animals 100mg/kg for extracts of *C. papaya* and *P. guajava*. For a combination of doses the extracts of *C. papaya* and *P. guajava* 100mg/kg mixed with 1:1.The fresh dose was prepared according to body weight of animals throughout

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the experiment. The pellets were dissolved in 1ml pure water then orally administered to animals by using the oral gavage.

Animals and Diet

A total twenty five healthy, adult male albino wister rats were choose for the study. The animal's body weight comprises around 150-200 g.

Induction of Diabetes

After acclimatization, the animals were fasted overnight for the induction of experimental diabetes. The diabetes was administrated by a single intra-peritoneal injection of 55 mg/kg body weight Streptozotocin (STZ) freshly prepared in 0.9% normal saline. The animals with blood glucose level > 200 mg/dl were designated as hyperglycemic and selected for the experiment.

Administration of Plant Extract

The animals were randomly divided into five groups (n=5) named as A, B, C, D and E according to similarity in their weight. Treatment was started from the third day after the injection of STZ. The plant extracts were fed once in a day at a specific time through oral gavage. The experimental groups were treated as following:

Group A: Served as the normal control group **Group B:** Served as untreated diabetic control group **Group C:** Diabetic rats were treated orally with *C. papaya* leaf extract at a dose of 100mg/kg body weight for 21 days respectively **Group D:** Diabetic rats treated orally with *P. guajava* leaf extract at a dose of 100 mg/kg body weight for 21 days respectively, **Group E:** It includes diabetic rats treated orally with combine leaves extract of *C. papaya* and *P. guajava* at a dose of 100 mg /kg for 21 days consecutively.

Body Weight and Glucose Level

The change in body weight and blood glucose levels of each animal was recorded at 0, 7, 14 and 21 days. The pre and post changes in weight and glucose level of diabetic and control group were observed.

Blood Collection

The experimental treatment was accomplished on 21 day. After that, the animals were fasted overnight but they had availability to water. On 22th day the animals were reweighed and anaesthetized by chloroform inhalation method. Blood samples were collected from heart by cardiac puncture method using sterile syringes and needles. The blood was drawn in vacutainer tubes with and without anticoagulant. The blood samples were retained at room temperature about 15 minutes for coagulation. Furthermore, blood was centrifuged at 5000 rpm for 5 minutes for serum collection. The centrifugation give raise a clear supernatant on the upper surface and precipitation of blood cells at bottom. All sera samples were placed in Eppendorf tubes and immediately stored at -20 C for the analysis of biochemical parameters.

Biochemical Analysis

Following biochemical parameters were determined through spectrophotometer method by using automated analyzer: Liver Function Test, Renal Function Test, Lipid profile Test and other tests included Blood glucose and Glycosylated Hemoglobin (HbA_1C).

Statistical Analysis:

All the data obtained from this study was evaluated statistically. Values were presented as Mean± SEM for five animals in each group. For statistical analysis, one-way ANOVA was performed using SAS ver. 9.1. The means of the values were compared using Duncan's Multiple Range Test (DMRT). Values with probability $p< 0.05$ were considered significant.

Results:

Body Weight

The body weight of rats were measured at the beginning and end of experiment. A slight increase in body weight of diabetic induced rats was observed after induction of diabetes. At the end of treatment period (21 days) significant decreased ($p>0.05$) in body weight of treated groups was observed when compare to initial body weight. In contrast, normal control and

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diabetic control group gained weight. The diabetic control group gain highest weight among all groups while treated groups show decrease in body weight in comparison with control group.

Organs Weight

The weight of liver, kidneys and pancreas were measured at the end of 21 days of experimentation. The rats of diabetic control group gain liver and pancreas weight as compare to other groups. The diabetic rats treated with *P. guajava* and *C. papaya* extracts showed no significant differences in the weights of kidney and pancreas among the different groups. However, the diabetic treated rats showed organs weight more similar to the normal group. Pancreas gained weight in case of normal control and diabetic control group. For treated groups, the effect of plants extract on pancreas was non-significant ($p > 0.05$). Values are expressed as Mean ± SEM of 5 animals for each group. The means with different superscript (a, b, c) are considered statistically significant at ($p<0.05$) as compared with diabetic control group (Table 1).

Parameters	Feeding groups					
	Normal control	Diabetic control	*Carica Papaya*	*Psidium guajava*	*Carica papaya +Psidium guajava*	P. Value
Liver (g)	6.20±0.100^{a}	7.85±1.050^{a}	5.90±1.662^{a}	6.866±1.013^{a}	6.100±0.200^{a}	0.8092
Pancreas (g)	0.55±0.05^{ab}	0.60±0^{a}	0.26±0.33^{c}	0.36±0.08^{bc}	0.30±0^{c}	0.0199
Kidney (g)	1.650±0.500	1.60±0^{a}	1.46±0.23^{a}	1.50±0.30^{a}	1.40±0^{a}	0.9486

Table 1: Effects of *C. papaya* and *P. guajava* extract on body organs weight of induced diabetic albino rats

Blood Glucose Level

The diabetic rats treated with *P. guajava* and *C. papaya* leaves extract at a dose of 100 mg/kg body weight for 21 days significantly reduced ($p< 0.05$) blood glucose levels (142.0±10.0, 158±54.4, 78.00±13.0) as compare to diabetic control group. However, the composite leaves extract (*P. guajava* and *C. papaya*) produce enormous hypoglycemic effect (78.00±13.0) as compare to individual plant extract. This show the protective effect of Plants extract in diabetes. A significant difference ($p< 0.05$) was observed between diabetic control and other groups at the end of experimental period.

Liver Function Markers

The activities of three most important liver enzymes ALT, ALP and AST, biomarkers of liver toxicity, are given in table 2. The streptozotocin-induction caused significant increase in plasma enzymes such as alanine aminotransferase (ALT), alkaline phosphate (ALP) and aspartate aminotransferase (AST) in diabetic rats. The treatment of diabetic rats with *P. guajava* and *C. papaya* extracts show non- significant reduction in hepatic enzymes ($p> 0.05$) with respect to control group. Besides, it was observed that *C. papaya* extract separately and composite form restore the level of AST (142.0±7.00, 156.0±31.0) similar to normal control group (Table 2).

Bilirubin and Gamma-Glutamyl Transferase

There was significant increase in level of GGT and Bilirubin in diabetic rats. The treatment of diabetic rats with *P. guajava* and *C. papaya* extract show non-significant change in GGT activity as compare diabetic control group. On the other, GGT level was restored when compare to normal control group. Similarly, the elevated level of bilirubin was significantly reduced ($p< 0.05$) by administration of *C. papaya* and *P. guajava* extract as mean values of treated groups are closely related to control group. Therefore, the raised level of bilirubin was

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restored by the treatment of plants extracts (Table 3).

Total Protein and Albumin

There is a non-significant change in total protein of all the treated groups.

Kidney Function Parameters

Both serum urea and creatinine levels were estimated to find out the effect guava and papaya leaf extract on kidney function. Initially, streptozotocin-induced diabetic groups showed a significant rise in creatinine and urea level as compare to normal control group. It was a sign of renal toxicity and dysfunction. In the diabetic group, the level of urea was increased significantly ($p<0.05$) as compared to the control group. While in treated groups, the urea level was reverted to a normal level as in the control group. However, a significant reduction ($p<0.05$) in creatinine level (0.250±0.50) was observed in contrast to diabetic control group (Table 3). Thus, the normal level of creatinine was restored.

Glycosylated Hemoglobin (Hba1c)

The activity of glycosylated hemoglobin is important marker for diabetes mellitus. Glycosylated hemoglobin <6 is consider to be normal. A significant increase in HbA_1C level in diabetic rats was observed as compare to control rats. The treatment of diabetic rats with *P. guajava* and *C. papaya* extract restored the level of glycosylated hemoglobin near to normal levels (Table 3).

Serum Lipid Profile

Diabetes was induced by injection of streptozotocin which is accompanied by hyperlipidemia. There high level ($p< 0.05$) of cholesterol, triglycerides, VLDL-C, LDL-C and low level of HDL-cholesterol observed in diabetic groups as compare to control group. The treatment of *P. guajava* and *C. papaya* leaves extract significantly lowers ($p< 0.05$) the elevated levels of serum triglycerides, VLDL-C, and LDL-C and as compare to diabetic control group. On the other, it did not change the serum cholesterol level whereas the level of HDL-C was raised as compare to diabetic control group. At the end of treatment period, the mean values of triglycerides and low density lipoproteins decreased to control values. The results supports the protective effects of plants extract in management of hyperlipidemia.

Parameters	Feeding groups					
	Normal control	Diabetic control	*Carica papaya*	*Psidium guajava*	*Carica papaya* +*Psidium guajava*	P. Value
ALT (u/L)	44.5±4.50^{a}	51.0±2.00^{a}	74.50±38.50^{a}	99.0±19.00^{a}	113.0±1.00^{a}	0.186
AST (u/L)	156.0±2.0^{a}	141.0±2.00^{a}	142.0±7.00^{a}	170.5±28.50^{a}	156.0±31.0^{a}	0.40
ALP (u/L)	117.5±3.5^{c}	186.5±7.5^{b}	221.3±26.0^{ab}	262.0±17.7^{a}	206.6±3.8^{b}	0.073
TP (g/dL)	6.8±0.05^{ab}	7.20±0.30^{a}	5.75±0.45^{b}	5.70±0^{b}	5.85±0.65^{ab}	0.104
Alb (g/dL)	34.6±1.45^{a}	32.4±1.45^{a}	36.85±3.45^{a}	35.55±1.75^{a}	28.45±4.55^{a}	0.424
Bilu (g/dL)	0.35±0.05^{b}	2.95±0.15^{a}	0.075±0.015^{a}	0.06±0.10^{ab}	0.06±0.05^{ab}	0.107
GGT (g/dL)	2.55±0.15^{a}	2.95±0.15^{a}	2.00±0.10^{a}	2.55±0.15^{a}	2.55±0.75^{a}	0.529

Table 2: Effect of *C. papaya* and *P. guajava* extract on hepatic markers of induced diabetic male albino rats. Values are expressed as Mean ± SEM of 5 animals for each group. The means with different superscript (a, b, c, d) are considered statistically significant ($p\leq0.05$) as compared with diabetic control group.

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Parameters	Feeding groups					
	Normal control	Diabetic control	*Carica papaya*	*Psidium guajava*	*Carica papaya* + *Psidium guajava*	P. Value
Urea (mg/dl)	24.50±1.50^{b}	77.00±9.0^{a}	38.500±25.00^{ab}	33.00±1.00^{ab}	36.00±8.000^{ab}	0.0471
Creatinine (mg/dl)	0.35±0.05^{b}	0.70±0^{b}	0.250±0.50^{b}	0.35±0.05^{a}	0.300±0^{b}	0.0054
HBA1C (%)	3.910±0.26^{a}	4.500±0.90^{a}	3.895±0.085^{a}	3.700±0.070^{a}	3.375±0.055^{a}	0.5040

Table 3: Effect of *C. papaya* and *P. guajava* extract on Renal Function Tests of induced diabetic male albino rats. Values are expressed as Mean ± SEM of 5 animals for each group. The means with different superscript (a, b, c) are considered statistically significant at ($p<0.05$) as compared with diabetic control group (Table 3).

Parameters (mg/dl)	Feeding groups					
	Normal Control	Diabetic Control	*Carica papaya*	*Psidium guajava*	*Carica papaya*+ *Psidium guajava*	P. Value
CHOL	49.0±2.00^{d}	91.5±3.50^{a}	55.0±3.00^{dc}	62.0±3.00^{bc}	67.0±3.00^{b}	0.0010
TG	123.50±2.50^{b}	16.00±3.00^{a}	112.50±1.500^{c}	105.0±3.500^{cd}	91.50±7.50^{b}	0.0049
LDL	15.82±1.51^{bc}	23.90±0.80^{a}	12.20±1.00^{c}	13.30±0.90^{bc}	16.93±0.44^{b}	0.0024
HDL	29.75±3.450^{a}	11.75±0.45^{c}	30.89±0.94^{b}	33.00±1.30^{a}	23.24±0.85^{b}	0.0018
VLDL	20.25±1.05^{ab}	27.95±1.45^{a}	18.40±3.70^{b}	19.90±2.20^{ab}	23.3±1.25^{ab}	0.1236

Table 4: Effect of *C. papaya* and *P. guajava* extract on Lipid profile test of induced diabetic male albino rats. Values are expressed as Mean ± SEM of 5 animals for each group. The means with different superscript (a, b, c, d) are considered statistically significant at ($p<0.05$) as compared with diabetic control group.

Discussion:

Diabetes is the world most growing health disorder. It is a biggest public health burden and minimum half a-billion of such cases are expected for the next decade. Two main factors which are responsible for diabetes include genetic factors and environmental factors. In most cases lifestyle play important role. The potential of medicinal plants have been revealed by a number of studies. Commonly, plants are exploited to cure diseases for their therapeutic effects. The present study was carried out to investigate the effects of *P. guajava* and *C. papaya* leaves extract on blood glucose, body weight, lipid profile and hepato-renal function of treated rats.

In this study, treatment with *C. papaya* and *P. guajava* extract showed decrease in body weight of treated group as compare to normal group and diabetic control group that gained weight. Diabetes mellitus causes a significant increase in body weight of diabetic rats as compare to normal group rats. It has been reported that weight loss is common symptom of diabetes mellitus. It is due to dysfunction insulin which inhibit the body utilizing glucose from the blood into body's cell. Meanwhile, the body start consuming fat and muscles for energy and led to reduction in overall body weight. The non-diabetic rats show higher body weight as they consume more water [9]. The weight loss occur due to hepatotoxic effect of *C. papaya* extract. The aqueous extract of *C. papaya* (0.75, 1.5 g/100 mL) caused a slight reduction in weight in diabetic rats [10].

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The results showed a significant increase in organs weight of diabetic control group as compare to normal control group. The treatment with Plants extract showed non-significant difference in kidney and pancreas weight. However, the weight of liver was restored like normal group (6.100±0.200). The reduction of organs weight may related to reduction in body weight [11]. It was reported that the guava leaf extract restored the liver weight in hepatotoxic rats [12].

The study revealed that diabetes caused significant increase in blood glucose level of diabetic-induced rats. The treatment with *P. guajava* and *C. papaya* extract significantly reduced ($p<0.05$) blood glucose level in treated group as compare to control group. The combine leaf extract show more hypoglycemic effect (78.00±13.0) in treated rats. The reduction in blood glucose is attributed by presence of quercetin in guava leaves. It promotes utilization of glucose in hepatocytes thereby lowers down hyperglycemia. The antioxidant ability of guava leaf extract, preserves beta cell function by neutralizing the free radicals generated by STZ [13]. Similarly, *C. papaya* improves insulin function in diabetic rats it is accompanied by glucose uptake by peripheral tissues and stimulate glucogenesis by liver and muscles [11].

In this study, the treatment of *P. guajava* and *C. papaya* extract did not reduce the activities of enzymes ALT and ALP and AST which indicate hepatotoxicity. The raised level of serum markers defines the extent of damage to hepatic parenchymal cells and micro-obstruction of bile ductules. Both plants extract have some constitutes which causes slight hepatotoxicity with the regulation of blood glucose level. The *C. papaya* and *P. guajava* extract at various dose may be hepatotoxic as the aqueous extract of *C. papaya* has the potential to cause liver damage in rats [14]. A study reported that at high dose of *P. guajava*, the liver markers especially AST level is increased [15].

In this Experiment, the administration of *C. papaya* and *P. guajava* extract in treated groups restored the levels of Albumin like control group. The Total proteins levels show non-significant changes after treatment of plants extract. The individual plants extract show more effect than composite extract. The *P. guajava* extract show no significant effect on serum total proteins in diabetic treated rats (Osman *et al.*, 2013). A study reported no significant change in total protein was observed in treated rats [14].

The present study showed the increase level of Bilirubin in STZ-induced diabetic rats. In treated groups, bilirubin level was normalize to control values after treatment with *C. Papaya* and *P. guajava* extract. It was reported by studies that insulin secretion is increased due to decrease in P-450 cytochrome in diabetic rats. The dysfunction insulin elevate heme oxygenase activity in liver. Plants extracts exert protective effects by improving insulin function that inhibit the catabolism of cytochrome P-450. The *C. papaya* fruit extract has ability to lower elevated bilirubin level [16].

Gamma-Glutamyl transferase (GGT) is a liver enzyme with antioxidant properties. The study showed administration of Plants extract in treated group restored the level of GGT like normal control group. This is due to free radical scavenging activities of plants extracts. [17]. The *C. papaya* leaf extract improve the level of GGT in dose dependent manner [14].

Hyperglycemia associated with impaired nitrogen level result in kidney damage. In this experiment, diabetic rats treated with *P. guajava* and *C. papaya* extracts show positive effect on creatinine level and non-significant effect for urea. The plants extracts produce beneficial effect regarding to regulate kidney function by reducing nitrogenous waste. The guava leaf extract improve creatinine and urea level in diabetic rats [18]. Similarly, a study reported *C. papaya* fruit extract restored the normal level of urea and creatinine [19].

Hyperglycemia indicates high level of gylcated hemoglobin. The study showed the treated

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groups administrated with *P. guajava* and *C. papaya* single and composite extract restored the normal level of glycosylated hemoglobin.

Liver function markers AST, ALP and AST are used to evaluate the function of liver. The increased activities of liver markers AST, ALT and alkaline phosphates (ALP) observed in diabetic rats caused by streptozotocin. The changes in liver enzymes and bilirubin indicate liver damage. Liver is a central house of metabolism. Hyperglycemia imposes oxidative stress on liver which result in disruption of carbohydrates, proteins and lipids metabolism. As a result reactive oxygen species (ROS) are generated which increase diabetic complications as well increase concentration of liver enzymes [18]. The study revealed that *C. papaya* and *P. guajava* extract exert hepatotoxic effect with the regulation of normal blood glucose level. Diabetes mellitus is associated with hyperlipidemia. The increased level of serum lipids in diabetes is substantial risk of coronary heart diseases. It is necessary to reduce serum lipids to prevent cardiovascular diseases [24].

The study revealed that STZ-induced diabetic rats have abnormal concentrations of serum lipids such as increased level of TG, LDL, VLDL and cholesterol and decrease level of HDL. The administration of *P. guajava* and *C. papaya* leaves extract significantly ($P<0.05$) restored the level of LDL, VLDL, Cholesterol and Triglycerides and increase in HDL level. The significant increase in HDL was observed which confirm the protective effect of plants extract against hyperlipidemia. The *C. papaya* extract reduced the atherogenic index in a dose-dependent manner show decreased LDL-C and increased HDL-C in serum significantly. *C. papaya* leaf extract ameliorate the elevated level of triglycerides by the activation of lipoprotein lipase which promote hydrolyses of triglycerides into fatty acid [10]. The *P. guajava* leaves and its isolated quercetin fraction have a hypolipidemic activity against CCl_4-induced hepatotoxic rats [18].

Conclusions:

The present study conclude that individual and combine plant extract show anti-hyperglycemic effect but the combine remedy at this dose show hepatotoxicity. The extract restored the normal function of kidney and show hypolipidemic effect.

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