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ASSESSMENTS OF PHYTOCHEMICALS AND HYPOGLYCEMIC ACTIVITY OF LEAVES EXTRACTS OF *CARICA PAPAYA* IN DIABETIC MICE

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ABSTRACT: Very little knowledge about use of papaya leaves is available in the literature, the leaves of papaya are bitter to taste which explains its therapeutic benefits. The present study was undertaken to assess anti diabetic effects of leaves extracts of *Carica Papaya* and Glucophage on streptozotocin –induced diabetic mice. Results indicates that hyperglycemic level in diabetic mice was normalized after administration of various doses (50, 150 and 300 mg/kg bw) of ethanolic leaves extracts to diabetic mice. Similarly leaves extracts of *C. Papaya* have also shown pronounced effects on plasma insulin, triglyceride, cholesterol and HDL cholesterol levels. The levels of liver enzymes (ALT, AST and ALP), bilirubin and blood cells (Red cells, white cells and platelets) were improved on dose depended manner. Analysis of various leaves extracts for phytochemicals revealed presence of significant amount of alkaloids, steroid, tannins, total phenols and flavonoids. It is assumed that biologically active components of papaya leaf extracts are helpful in decreasing secondary complications of diabetes and improved insulin sensitivity to uptake glucose by cells. Which also indicates that these extracts might be good source of pharmaceutical materials need for preparation of various drugs required for human health.

INTRODUCTION: The consumption of fruits and vegetables has increased in recent years due to their health benefits [1]. Fruits and vegetables being rich in bioactive compounds help to lower the incidence of many diseases including diabetes types 2 [2]. Diabetes mellitus is the probably world's largest metabolic disorder that is steady growing in human population throughout the world [3].

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Diabetes is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both [4]. Therapeutic options for diabetes are diet, exercise, oral hypoglycemic drugs and insulin therapy. These drugs have been used as monotherapy or in different combinations so as to control diabetic condition but search for newer drugs continues because of the various limitations of the synthetic drugs.

The world health organization has been particularly attentive to the potential offered by herbal medicines, the main subfield of traditional medicines practiced in different countries [5]. The

medicinal plants have immensely contributed to health needs of humans throughout their existence and role of medicinal plants as producer of drugs is not controversial today. It was reported that secondary metabolites available in plants have therapeutic properties and have drug development potential [6]. Furthermore phytotherapeutics are not alternatives but part of modern medicines. Medical doctor prescribes both synthetic drugs and phytotherapeutics and patients takes medicines to regain their health [7]. The significance of plant based medicines have been increased all over the world and about 50 % medicines available in the markets are made up by plants based active ingredients whose alternative cannot yet be prepared synthetically [8].

Carica papaya (papaya) belongs to family Caricaceae distributed throughout the tropics and subtropics countries of the world. It is a tree like herbaceous plants and cultivated for its edible utilization [9]. The leaves, fruits and seeds of papaya contained phenols, flavonoids, carotenoids, essential vitamins and minerals [3]. Papaya seeds are thought to contained some antioxidant agents [10]; the pulp is being used for treatments of wounds and burns, latex and seeds for relief of gastrointestinal problems. Whereas leaves are used to relieve the problems of asthma, fever and amoebic dysentery. Chemical analysis of *C. Papaya* plant tissues indicates presences of cysteine endopeptidases, a class- 11 and calss-111 chitinase and glutaminlycyclase in the latex, the linalool in fruit pulp [3]. The alkaloids carpaine, pseudocarpaine, dehydrocarpaine I and II, the cyanogenic compounds in leaves and roots and benzylglucosinolate and its metabolites in all tissues. The aim of this work was to assess, antidiabetic effects and screening of phytochemicals from leaves of *C. papaya*.

MATERIALS AND METHODS:

Plant material: Leaves samples of *C. papaya* were collected from Rawalpindi in August 2014 and identified by expert and voucher specimen was deposited in the herbarium (No. 137) for future reference. Leaves samples were shadow, sun dried followed by oven drying for overnight at 50^{o}C and then ground into powder form and finally freeze dried at -20 ^{o}C until analysis.

Chemical products:

STZ were purchased from Sigma Aldrich (St Louis, MO, USA). Boehringer Mannheim GmbH kit (ELISA- Principle) was used for insulin assay. All chemical reagents used in this experiment were of A grade and obtained from Merck. Whereas kits for different enzymes assays were purchased from Randox GmbH (Germany).

Assays:

Total 50 g dried and ground leaves samples of *C. Papaya* were separately placed in 500 ml round bottle flask. The maceration and extraction of samples were carried out with n-hexane, chloroform, methanol and ethanol at room temperature. These extracts were used for quantitative estimation of alkaloids, steroid and tannins [11, 12] and values were expressed as mg/ g of leaves extracts Total phenolic contents of extracts were determined by using Folin-Ciocalteu reagent [13] and standard solutions of gallic acid was used for calibration curve. The total phenolic contents were expressed as milligrams of gallic acid equivalent (mg GAE/g) of leaves extract. The amounts of flavonoids contents in leaves extracts was quantified [14]. The standard solution of quercetin was used for calibration cure and total flavonoids contents of extracts were expressed as milligrams of quercetin equivalents (mg QE/g) of leaves extract.

Determination of flavonoids with HPLC:

The ethanolic leaves extracts which has shown higher amounts of total flavonoids was further quantified with higher performance liquid chromatography by using isocratic elution, with methanol and water mixture (70:30) with flow rate of 1 ml/min, retention time of 20 min and by providing 20 µl sample to C18 column at 30^{o}C and amount of quercetin (flavonoid) was quantified by using UV/visible, detector at 368nm wavelength.

Preparation of *C. Papaya* leaves extracts for animal study:

Dried leaves sample (I00 g) were placed in the Soxhlet system and extraction was carried out for 5 h with 500 ml of ethanol, after words the solvent was evaporated under vacuum until the extract was completely dried and was preserved at lower

temperature (-20 ^{o}C). The ethanolic leaves extract of *C. Papaya* at final concentration of 1 mg/ml was used for pharmacological assays [3].

Animals:

Swiss albino mice of either sex (60 to 65 g) were used in this experiment. Mice were acclimatized and maintained individually in cages in an air conditioned room at 22 ± 2 ^{o}C for one week prior to the experiment in the conventional animal house. The care and handling of these mice were in accordance to internationally accepted standard guidelines for animals handling. Mice were given standard laboratory diet with free access to water *ad libitum* and during experimental period no physical stress was given and number of animals used was reduced as possible. The experimental protocol was approved by Ethical Committed of the Arid Agriculture University constituted for animals study.

Induction of diabetes:

Diabetes was induced to overnight fasted animals by a single intraperitoneal injection of streptozotocin (80 mg/kg body weight) freshly dissolved in 0.1 M citrate buffer (pH 4.5). Only diabetic animals, whose hyperglycemia level (≥198 mg/dl) was confirmed by measuring the serum glucose level after three days of injection were included in this experiment. The hypoglycemic effect of leaves extract of *C. papaya* was determined by providing, 50, 150 and 300 mg/kg of ethanolic leaves extracts orally in 300 µl of polyethylene glycol.

Thirty mice were divided into six group of five each (n-5) Group 1; Negative control (vehicle) was given 0.8 ml of citrate buffer (0.1 M, pH 4.5) /Kg bw of mice. Group 2; Positive control (diabetic mice) received 2 ml of ethanol only. Group 3; Animal of this group received 50 mg/ kg bw of ethanolic leaves extracts of *C. Papaya.* .Group 4; Animals of this group received 150 mg/kg bw of ethanolic leaves extracts of *C. Papaya*. Group; 5 Animals of this group received 300 mg/kg bw of ethanolic leaves extracts of *C. Papaya*. Group 6; Animals of this group received 1 mg /kg/b.w of standard anti diabetic drug (Glucophage). The body weight of each group of animals were determined at 0 day and after 10 days of treatments by using electrical balance. At the end of the experimental all mice were sacrificed, serum was collected; liver was removed and washed with ice cold physiological saline. Organs were homogenized in 0.1M trisHCl buffer (pH 7.4) to give a 10% homogenate. This homogenate was used for the estimation of blood glucose level, triglyceride, HDL and LDL cholesterol by using commercial kits (Randox Laboratory) and enzymatic method of Hafiane and Genest [15]. The Plasma insulin level was assayed by using enzyme linked immune sorbent (ELSIA kit) [16].

The enzymes Alanineaminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin was estimated by using their respective diagnostic kits and Auto-analyzer (Merck) [17]. Whereas body weight of animals was calculated by measuring weight before and after treatments with leaves extracts.

Statistical analysis:

All data are expressed as mean ± S.E. ANOVA was performed followed by DMRT to comare the difference between the treatments. Differences were considered statistically significant for $p< 0.05$.

RESULTS:

Phytochemicals analysis of leaves extracts:

Leaves samples of *C. Papaya* were analyzed for alkaloids, steroids, tannins, total phenol and flavonoids contents and results are presented in **Table 1**. According to results, ethanolic leaves extract contained higher amount of alkaloids (1.57± 0.3 mg/g), steroid (0.74± 0.5 mg/g), tannins (0.69/± 0.2 mg/g), flavonoids (49.05 ±1.14 mg QE /g) and total phenols (54.23 ±1.18 mg GAE /g). Whereas concentration levels of these parameters were lower in other Leaves extracts and due to this reason ethanolic leaves extract was further used for pharmacological study of animals.

Analysis of Flavonoids (Quercertin) from leaves extracts with HPLC:

Analysis of ethanolic leaves extracts of *C. Papaya* with higher performance liquid chromatography was carried out. Comparison of peaks obtained by analysis of standard quceretin(**Fig. 1**) and leaves extracts (**Fig. 2**) revealed that *C. Papaya* leaves contains higher amount of quceretin (flavonoid).

It was reported by many authors including Canini et al[18] that many flavonoids including quercetin are available in leaves of *C. papaya* samples however, quantity found by them was lower as compared to amount of quceretin obtained in current study.

TABLE 1: ASSESSMENT OF SELECTED SECONDARY METABOLITES FROM LEAVES EXTRACTS OF *C. PAPAYA*

Extracts	Alkaloids mg/g	Steroid mg/g	Tannins mg/g	Flavonoids (mg QE /g)	Total phenols (mg GAE/g
Ethanolic leaves extract	1.57 ± 0.3*	0.74± 0.5*	0.69± 0.2*	49.05± 1.14 *	54.23 ± 1.18*
Methanolic leaves extract	1.21± 0.3	0.56± 0.1	0.72± 0.2	38.15 ± 0.24	48.66 ± 1.52
n-hexane leaves extract	0.53± 0.1	0.38± 0.2	0.49± 0.1	31.15± 2.15	35.14± 0.73
Chloroform leaves extract	0.64± 0.3	0.47± 0.1	0.54± 0.3	44.29± 2.14	45.25 ± 1.14

Values are represent as mean ± SD (n=3), Significantly higher values (P<0.05) as compared to other extracts

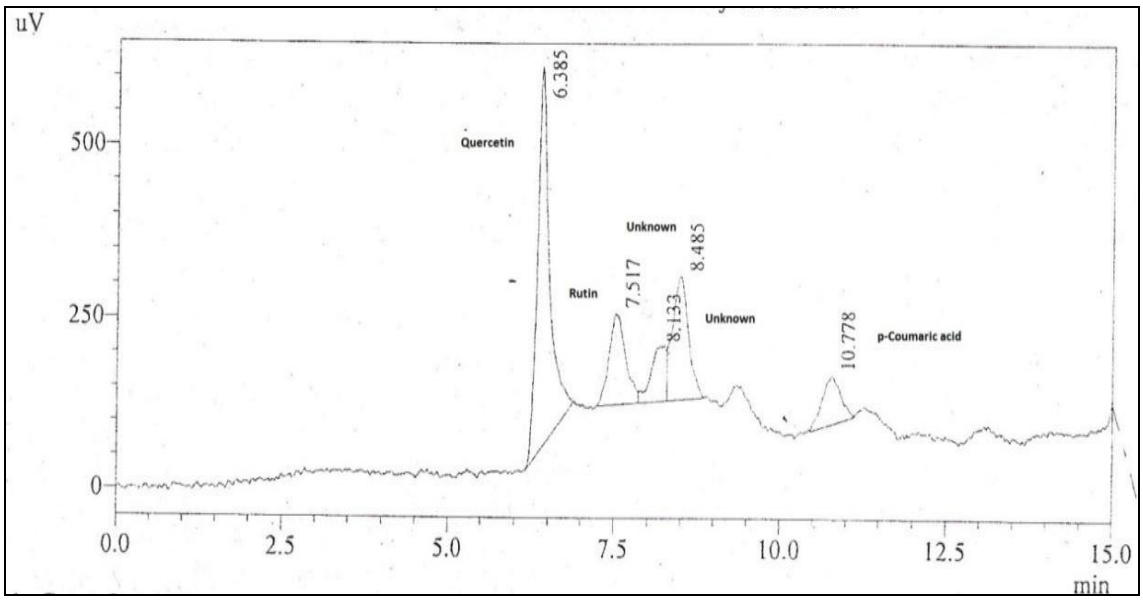

FIG. 1: HPLC ANALYSIS OF STANDARD QUERCETIN

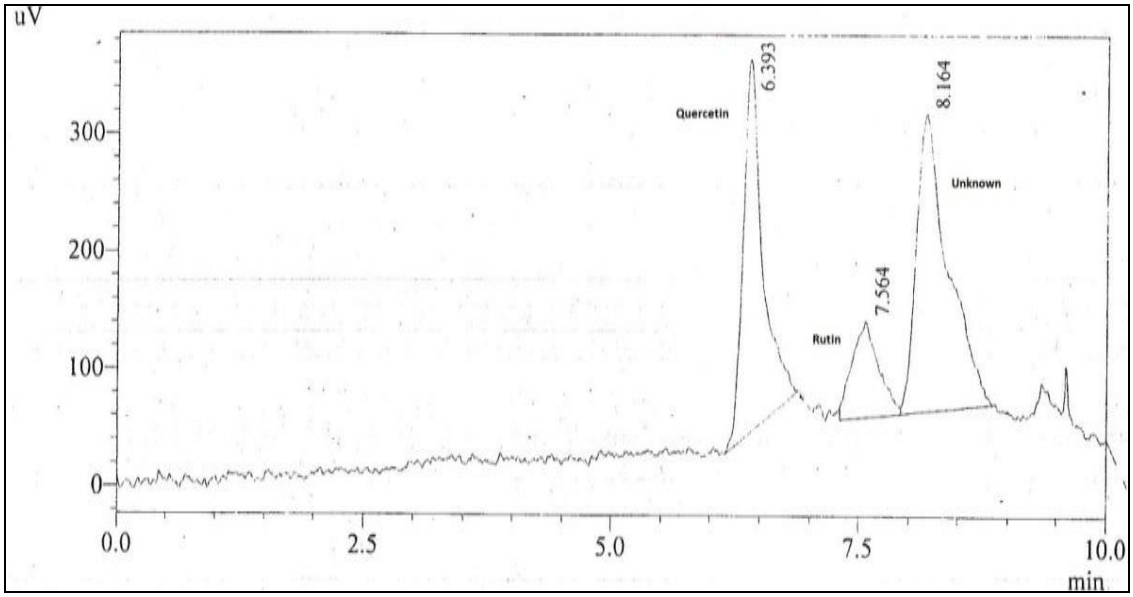

FIG. 2: HPLC ANALYSIS OF ETHANOLIC LEAVES EXTRACTS OF *C.PAPAYA*

Analysis of various parameters related to diabetes:

Weight of animals: It was observed that by induction of diabetes, body weight of animals was slight increased, which was further normalized after treatment with various doses of ethanolic leaves extracts of *C. Papaya* (**Table 2**).

TABLE 2: EFFECT OF *C. PAPAYA* EXTRACTS ON BODY WEIGHT OF STZ DIABETIC MICE.

Group	Treatment	Initial weight (g)	Final weight (g)
1	Diabetic mice	62.11±0.32	63.24 ±0.54
2	Treated with ethanolic leaves extracts 50 mg/kg bw	63.02 ±1.34	62.53±0.37
3	Treated with ethanolic leaves extracts 150 mg/kg bw	63.13 ±0.35	61.21 ±0.34
4	Treated with ethanol leaves extract 300 mg/kg/bw	63.01±1.15	60.68±1.31*
5	Treated with Glucophage 1 mg/kg bw	64.39 ± 0.61	61.11 ±1.21

*Significant ($p<0.05$) compared with control/normal. Values are expressed as mean ±SE. Weight of normal animals 60-65 g.

Hyperglycemia:

STZ-induced diabetes in mice resulted in a significant increase in serum glucose levels (197.84±1.65 mg/dL) in comparison to the control group (101.25±1.61 mg/dL) ($p< 0.05$). After the administration of different doses of the ethanolic leaves extract of *C. papaya* (50,150 and 300 mg/ kg, b.w) to diabetic mice upto 10 days a significant decrease in blood glucose level (101. 48 ± 0.29) was observed as compared to hyperglycemic level in diabetic animals (197.84±1.65 mg/dL) and standard drug Glucophage (101.34±2.65 mg/dL) (**Table 3**).

TABLE 3: EFFECT OF VARIOUS EXTRACTS ON BLOOD GLUCOSE LEVEL (mg/dL) IN FASTED MICE.

Group	3rd day	5th day	7th day	10th day
Group1, +0.4ml citrate buffer (Negative control	101.25±1.61	102.34±1.32	99.23±0.32	98.23±1.21
Group 2.+2ml ethanol (Positive control)	197.84±1.65	191.18±1.23	184.27±1.32	176.15 ±1.67
Group 3 + 50 mg/kg ethanolic leaves extracts	191.52±1.34	186.21±1.15	163.39±1.73	157.54±0.25
Group4 ,+150 mg/kg ethanolic leaves extract of *C.Papaya*	145.15±1.61	138.21±1.41	117.17±1.64	113.65±1.23
Group 5 ,+300 mg/kg ethanolic leaves extract of *C.Papaya*	131.12±1.21	108.52±2.42*	105.18±3.52	99.18±0.23*
Group5,+1mg/kg/b.w Glucophage	107.21±1.56	103.21±1.36	103.34±1.52	101.34 ±2.65

*Significant reduction in blood glucose level (($p< 0.05$) of animals treated with 300 mg/kg bw of ethanolic leaves extracts as compared to control/normal. Values are expressed as mean ±SE.

Lipid profile:

It was observed that triglyceride and serum cholesterol levels were increased, whereas HDL cholesterol level was decreased in diabetic animals as compared to normal vehicle. However, after administration of 300 mg/kg ethanolic leaves extracts significant ($P < 0.05$) changed was observed and these values turned towards normal (**Table 4**).

TABLE 4: EFFECTS OF LEAVES EXTRACTS ON LEVEL OF LIPID PROFILE IN NORMAL AND STZ INDUCED DIABETIC MICE

Group	Treatment	Insulin ng/ml	Triglyceride (mg/dL)	Cholesterol (mg/dL)	HDL cholesterol (mg/dL)
1	Normal (vehicle)	1.06±0.2	94.13±1.15	68.13 ±1.51	48.23±1.38
2	Diabetic control	0.67±0.1	127.24±1.56	105.34± 1.16	45.44 ±1.28
3	Ethanolic leaves extract (50 mg/kg)	0.77±0.16	121.31±1.38	97.29±2.18	44.58 ±1.55
4	Ethanolic leaves extract (150 mg/kg)	0.86±1.58	97.26 ± 1.62	86.38± 0.77	46.65±1.58
5	Ethanolic leaves extracts (300 mg/kg)	0.98±0.12 *	93.81±2.37*	69.28±1.16*	49.29 ±1.41*
6	Glucophage(1 mg/kg)	0.98±0.5	95.38± 2.76	64.34±1.32	48.24 ±2.35

Significant ($P <0.05$) values vs control /normal and expressed as mean ± SE, n=5

Liver enzymes:

The effects of leaves extracts on liver enzymes of diabetic and normal mice were observed. According to results, significant raised in the level of ALT, AST ALP and total bilirubin in diabetic animals as compared to animals in negative control group was observed (**Table 5**).

TABLE 5: EFFECTS OF *C. PAPAYA* LEAVES EXTRACTS ON LIVER ENZYMES IN MICE.

Groups	ALT (U / L)	AST (U / L)	ALP (U / L)	Total Bilirubin(mg/ dL)
Negative control	41.95±1.56	57.19±1.34	65.51±1.28	0.15±0.01
Positive control	62.89±1.58	78.13±0.86	93.91±1.81	0.39±0.02
Ethanolic leaves extracts (50 mg/kg)	58.85±1.07	68.56±1.49	82.53±2.54	0.37±0.08
Ethanolic leaves extracts (150 mg/kg)	47.28±1.57	59.05±1.07	74.16±2.61	0.21±0.04
Ethanolic leave extracts (300 mg/kg)	45.98±3.85*	56.82±1.19*	64.09±1.31	0.18±0.05
Glucophage(1 mg/kg)	43.57±1.28	55.32±1.65	63.15±1.34	0.14±0.02

Values are expressed as mean ± S.D (n=5);*significant difference from control group ($p<0.05$) and standard drug ($p<0.05$).

Blood cells:

The levels of blood cells were changed by induction of diabetes and administration of 300 mg/kg of ethanolic leaves extract to mice improved the levels of these parameters at passage of time and became closed to normal (**Table 6**). It is demonstrated that *C. Papaya* leaves contained bioactive compounds those are effective against elevated level of blood cells and have potential to improve the level of these cells and bring them towards normal.

TABLE 6: EFFECTS OF VARIOUS EXTRACTS OF *C. PAPAYA* ON BLOOD CELLS.

Groups	RBCs (10^6 / mm^3)	WBCs (10^3 / mm^3)	Platelets (10^3 / mm^3)
Negative control	4.93±0.46	5.59±0.81	259.35±2.89
Positive control	4.19±0.65	4.73±0.45	234.15±2.74
Ethanolic leaves extracts (50 mg/kg)	4.58 ±0.32	4.81±0.23	238.64±1.65
Ethanolic leaves extracts (150 mg/kg)	4.65±0.28	4.97±0.58	247.71±1.05
Ethanolic leaves extracts (300 mg/kg)	4.88±0.17 α	5.56±0.38 α	254.62±1.81 α
Glucophage(1 mg/kg)	4.62±0.39	5.52 ±0.24	2.56±1.24

Values are expressed as mean ± S.D (n=5);*significant difference from control group ($p<0.05$).

DISCUSSION: The ethanolic leaves extracts of *C. Papaya* provided higher amount of total phenol and flavonoids as compared to other extracts analyzed (**Table 1**, **Fig. 1** and **2**). Whereas results of phytonutrients obtained in current study were comparable with results reported by Indran et al.[19]. Phenolic compounds are secondary metabolites present in all plants in wider range, possess free radical scavenging activity and considered as potential antioxidant agents having great impact on human health [20]. The concentration level of flavonoids found in *C. papaya* leaves samples obtained during present study was higher than reported by Omotade et al.[21]. Flavonoids possess antioxidants, antiviral, antifungal and antibacterial activities but also protect liver and stomach from different disorders. Quercetin is a flavonoids found in leaves extracts of *C. papaya* (**Fig. 1** and **2**), prevents human body from releasing histamines that cause an allergic response in the body. Quercetin also prevents plaque build-up in arteries (atherosclerosis) that can lead to heart attack, stroke, and obesity [22].

Diabetes mellitus is one of the most common chronic diseases associated with carbohydrate metabolism. It is also an indication of co-morbidities such as obesity, hypertension, and hyperlipidemia which are metabolic complications of both clinical and experimental diabetes. In this work hypoglycemic activity of ethanolic leaves extract of *C. Pappaya* was evaluated in streptozotocin induced diabetic mice. According to different studies conducted, STZ destroys

pancreatic insulin secreting β cells by causing diabetes close to type 2 diabetes in animals. However, treatments of animals with ethanolic leaves extracts for ten days has shown significant improvement in STZ induced diabetic animals. The number of functionally intact β cells in the islet organ is of decisive importance for the development course and outcome of DM. The total β-cell mass reflects the balance between the renewal and loss of these cells [23]. Ethanolic leaves extracts of *C. Papaya* showed hypoglycemic activity either by acting. On the activity of pancreatic beta cells and increase in the inhibitory effect against insulinase enzyme and increase of the insulin sensitivity or the insulin like activity of the leaves extracts. According to results weight of animals was increased after induction of diabetes as compared to control group.

However, weight of animals was normalized after treatment with ethanolic leaves extracts (**Table 2**). The extracts treated animals recovered the body weight significantly toward normal level which may be due to the lipid lowering activity of the extract or indirectly to the influence on various lipid regulation systems [24]. Furthermore reduction in glucose level was observed in diabetic mice as compared to the vehicle control group (**Table 3**). The decrease in blood glucose level may be due to potentiation of insulin effect either by increase in pancreatic secretion of insulin from beta cells, islets of Langerhans or by increase in peripheral glucose uptake [18]. Furthermore observed hypoglycemic effects of leaves extracts may be due to inhibition of fatty acid synthesis and decreased of cholesterogenesis, because increasing amount of these parameters, further increase risk of obesity and diabetes [5]. In diabetes mellitus development of polyuria, polydipsia and polyphagia symptoms are possible [4].

A significant increase in serum cholesterol, triglyceride, bilirubin and decrease in HDL cholesterol was observed in STZ induced diabetic mice, when compared to vehicle control. However, on administration of 50, 150 and 300 mg/kg of ethanolic leaves extracts to the diabetic mice, lipid profile level was found to be restored and turned to words normal level (**Table 4**) and results were comparable with results reported earlier by Del et al.[7]. Significant reduction in levels of ALT, AST and ALP were found in animals treated with ethanolic leaves extracts (**Table 5**). Results were significant ($P < 0.05$) at three doses however, better results were obtained by treating animals with 300 mg/kg of leaves extracts. ALT, AST and ALP are important liver enzymes and if levels of these enzymes in body are not at normal condition then many disorders relevant to liver are possible [25]. The levels of RBC, WBC and blood platelets were reduced by induction of STZ in experimental animals but after treatments of animals with ethanolic leaves extracts levels of blood cells restored and turned towards normal (**Table 6**).

Red blood cells contained important proteins hemoglobin and if level of this protein decreases then anemia and other complication may raises in the body [20]. Whereas due to low white blood cells either by chemotherapy or viral diseases leukopenia can occur, whereas due to lower platelets count, thrombocytopenia is possible which is another health disorder in human population [26]. Ethanolic leaves extracts also improved levels of these blood cells and turned towards normal (**Table 6**). Which indicates that might be leaves of *C. Papaya* contain phytonutrients those have beneficial effects on blood cells. The results of this study were satisfactory and revealed that the ethanolic leaves extracts of *C. Papaya* exhibited hypoglycemic activity.

CONCLUSION: The ethanolic leaves extract of *C. Papaya* demonstrated significant hypoglycemic activities in STZ induced diabetic mice. The extract showed improvement in various body and serum parameters as well as regeneration of β cells of pancreas that might be of valuable for treatments of diabetes. However, further phytochemical investigations are required to isolate and identify the hypoglycemic principles in this leaves extracts as well as elucidating their mechanism of action.

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