



Research Article

PANCREATIC PROTECTIVE AND THERAPEUTIC EFFECT OF *ARACHIS HYPOGAEA* SKIN EXTRACTS AGAINST CARBON TETRACHLORIDE (CCl₄) IN MICE

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ABSTRACT

The aim of this investigation was to assess the influence of peanut (*Arachis hypogaea*) skin extracts on pancreatic protective and therapeutic effects and reduce the level of blood glucose on laboratory animals damaged by Carbon Tetrachloride (CCl₄). The study began with the collection of seed coats, maceration and Soxhlet apparatus were used to prepare aqueous and methanolic extracts respectively, phytochemical detection, and acute toxicity of peanut skin extracts and antidiabetic testing of male mice with the carbon tetrachloride (CCl₄). Forty male albino mice were randomly divided into ten groups of four animals each. The experiment was conducted in two methods: pre-treatment groups and post-treatment groups. The results showed that the serum blood glucose level was significantly increased ($p < 0.01$) in the CCl₄ treated group (group 2) of mice (172.00 ± 2.08 mg/dl) compared with the control group (group 1) (101.43 ± 2.02 mg/dl) indicating the induction of severe pancreatic toxicity. The best effect in the level of serum blood glucose was in methanolic treated groups 100 mg/kg (Group 4 and 8) (104.27 ± 2.07 and 107.10 ± 1.75 mg/dl) respectively in both pre and post-treatment when compared with the control group. The histopathological examination of pancreas obtained from mice with administrated CCl₄ showed fatty changes in the cells of islet and depletion of secretion, while when treated with 100 mg/kg of methanolic extract revealed the islets of pancreas look like normal structure appearance.

Keywords: *Arachis hypogaea* L., pancreatic protective, blood glucose level, CCl₄.

INTRODUCTION

Diabetes mellitus is still one of the most important causes of death and disability in both developed and developing countries. Diabetes mellitus is a metabolic disorder affecting the body's ability to make or utilize insulin, a pancreatic hormone that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel. The disease results in abnormal levels of glucose in the bloodstream¹. Hyperglycemia, increased water intake and polyurea are the main indication of diabetes mellitus². Free radicals, produced by carbon tetrachloride (CCl₄), have been widely used to induce insulin deficiency in experimental animals and cause necrosis of pancreatic b-cells³. The induction of CCl₄ leads to increase in the generation of reactive oxygen species (ROS) inhibits free radical scavengers and causes lipid peroxidation and DNA damage^{4, 5}. Antioxidants play an important role in preventing or, in most cases, limiting the damage caused by free radical. Healthy people and animals possess many endogenous antioxidative substances that scavenge free radicals *in vivo* to maintain the redox balance and genome integrity⁶. Phytochemicals have always been an important source of remedies for human health problems. Numerous experimental and clinical studies have documented beneficial effects of phytotherapy for managing diabetes⁷. Peanuts are as rich in antioxidants as many fruits⁸. Peanut is a dietary source of biologically active polyphenols such as the stilbene, trans-resveratrol, flavonoids such as the proanthocyanidins, and flavonols such as quercetin⁹. Most of the antioxidants are located in the skin of peanuts¹⁰.

MATERIALS AND METHODS

Chemicals

All chemicals used for extraction and detection of plant were analytical grade and were obtained from Sigma/Aldrich Chemical Company, St. Louis MO, USA. Standard Kit for assay the serum level of glucose purchased from (Cecil, Spain). Cecil

Plant material

Raw peanut pods were purchased from the local market in Baghdad city and classified as *Arachis hypogaea* L. by the herbarium of the Biology Department, College of Science, University of Baghdad. Pods were manually shelled, and the seed coats were collected from the raw peanut kernels. The seed coats were ground using a grinder and stored at -20°C for future analysis.

Preparation of aqueous extract

Water extract was prepared according to N'Guessan *et al.*¹¹. Macerated 100 gram of peanut skin in 1000 ml of distilled water for 72 hours, after extraction, the mixture was vacuum filtered through Whitman No.1 paper and the filtrate were dried at 50°C by a rotary evaporator. The resulting extract stored in amber glass vials at 4°C until analyzed. The whole process was completed under dim light to minimize light induced degradation of phenolics, which are generally light sensitive.

Preparation of methanolic extract

Soxhelt apparatus was used to prepare methanolic extract. 50 grams of peanut skin was put in a thimble and 350 ml of methanol was added within 40-60 °C for 6 hours. The solution has been filtered through a filter paper Whitman No.1 and evaporated to dryness under vacuum at 40°C, the dried extract have been weighed and stored in amber glass vials at 4°C until analyzed ¹².

General chemical detection methods

Methanolic and aqueous extracts were tested for the presence of the phytoconstituents according to the following standard tests to detected flavonoids, phenols, alkaloids, tannins, glycosides and saponin ^{13, 14}.

Acute toxicity test

The acute toxicity of peanut skin extracts was tested in mice, which were dosed in a stepwise procedure using the fixed doses of 100–2000 mg/kg orally according to the OECD guideline No. 420 ¹⁵. The animals were fasted overnight and then received peanut skin extracts. The animals were then observed for 3 hours for general behavioral, neurological, and autonomic profiles and every 30 min for the next 3 hours and finally for mortality after 24 hours.

Experimental animals

Forty male albino mice weighing 35 ± 5 g were obtained from Biotechnology Research Center, AL- Nahrain University. They were kept in standard conditions, the temperature about 22°C, 12 hours light/dark cycle. The animals were acclimatized for one week before starting the experiment. The experimental protocols were approved and carried out according to guidelines for the use and care of experimental animals.

Experimental design

The forty mice were randomly divided into ten groups of four animals each. The experiment was conducted in two methods: **pre-treatment** groups and **post-treatment** groups.

Group 1: This group served as a negative control in which the mice received normal feed and distilled water for 35 days

Group 2: This group was a positive control for CCl₄, which induce pancreas damage in mice. CCl₄ was solved in olive oil with ratio (1:3) (CCl₄: olive oil) at a dose of 3 ml/kg injected intraperitoneally (i.p.).

Group 3: This group was the pre-treatment group, in which the mice were administered with 50 mg/kg methanolic extract orally for 35 days and injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 35 day.

Group 4: This group was the pre-treatment group, in which the mice were administered with 100 mg/kg methanolic extract orally for 35 days and injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 35 day.

Group 5: This group was the pre-treatment group, in which the mice were administered with 50 mg/kg aqueous extract orally for 35 days and injected (i.p.) 3 ml /kg of CCl₄ and olive oil mixture on the 35 day.

Group 6: This group was the pre-treatment group, in which the mice were administered with 100 mg/kg aqueous extract orally

for 35 days and injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 35 day.

Group 7: This group was the post-treatment group in which the mice were injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 1st day and received 50 mg/kg methanolic extract orally for 35 days.

Group 8: This group was the post-treatment group in which the mice were injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 1st day and received 100 mg/kg methanolic extract orally for 35 days.

Group 9: This group was the post-treatment group in which the mice were injected (i.p.) 3 ml/kg of CCl₄ and olive oil mixture on the 1st day and received 50 mg/kg aqueous extract orally for 35 days.

Group 10: This group was the post-treatment group in which the mice injected (i.p.) with 3 ml/kg of CCl₄ and olive oil mixture on the 1st day and received 100 mg/kg aqueous extract orally for 35 days.

Collection of blood

Blood samples were collected at the end of the experiment; the mice were anesthetized with the injection of 200 µl (160 µl ketamine 10% + 40 µl xylazine) of anesthesia agent. Then their abdominal areas were opened, and the blood samples were directly taken from their hearts. The blood sample was rocked slightly and centrifuged at 3000 rpm for 5 minutes. The serum was then stored in the freezer at -21°C until analyzed ¹⁶.

Histopathological examination

At the end of the experimental period (35 days), mice were anesthetized and sacrificed; the pancreas of different groups was removed and kept in 10% formaldehyde solution; stained with hematoxyline and eosin (H&E) for histological examination ¹⁷.

Statistical Analysis

The statistical analysis system program was using to study different parameters. LSD test was used to significant compare between means in this study ¹⁸.

RESULTS AND DISCUSSION

Phytochemical detection of *Arachis hypogaea* skin extracts

The phytochemicals detection results are shown in (Table 1) which indicates the presence of flavonoids, phenols, alkaloids, tannins and glycosides in methanolic extract, while alkaloids gave a negative test in aqueous extract. *Arachis hypogaea* skin extracts showed contains a number of phytochemicals such as flavonoids and other polyphenols ¹⁹. Moreover, earlier study revealed the presence of flavonoids; phenols and coumarins in methanolic extract and the other phytochemicals tannin, saponin, alkaloids were present in trace amounts ²⁰.

Acute Toxicity of *Arachis hypogaea* Skin Extracts

The study of acute toxicity of *Arachis hypogaea* skin extracts shows different signs when treated with different oral doses of aqueous and methanolic extract (Table 2). The experimental mice show appreciable changes in physical activity and shown abnormal responses such as Tacky cardiac, increase breathing, sedation and animal tend to loneliness for one side in different

time in dose 2000 mg/kg, but there is no mortality in mice were recorded after 24 hours post treatment. The results showed that the aqueous and methanolic skin extracts of *Arachis hypogaea* practically non toxic according to Hodge and Sterner²¹ as shown in (Table 3). Toxicity tests are not designed to study the safety of these plants, but to point the toxic effects that can produce²², but to determine the safety margin of the extract. Accordingly, to this study, both extracts of *Arachis hypogaea* erectus did not induce lethality in mice when administered orally at doses of began from 100 till reach to 2000 mg/kg. This result suggests that LD50 of the extract would be greater than 2000mg/kg²³. Therefore, the plant extract can be assumed practically non-toxic²⁴.

Effects of peanut skin extracts on blood glucose level in mice

The serum blood glucose level was significantly increased ($p < 0.01$) in the CCl₄ treated group (group 2) of mice (172.00 mg/dl) compared with the control group (group 1) (101.43 mg/dl) indicating the induction of severe pancreatic toxicity. Yavar *et al.*²⁵ observed that CCl₄ injection significantly increases blood glucose level in damaged rats. It has been reported that excess cellular ROS can cause the perturbations in mitochondrial function and play a role in the pathogenesis of diabetes complications²⁶. The generation of ROS in response to the high concentrations of glucose may also cause mitochondrial dysfunction and trigger β -cells apoptosis²⁷. The elevation of glucose level could be by decreasing the pancreatic secretion of insulin from β -cells of islets of langerhans because of fatty changes in the cells of islet resulting from the toxicity of CCl₄.

The first method (pre-treatment) Treatment with methanolic extract 50 mg/kg (Group 3) showed significant decrease ($p < 0.01$) in concentrations of serum blood glucose level (112.60 mg/dl) compared with the CCl₄ treated group. The best effect in the level of serum blood glucose was in methanolic treated groups 100 mg/kg (Group 4) (104.27 mg/dl) when compared with the control group as shown in (Table 4). Furthermore, the levels of serum blood glucose were significantly decrease ($p < 0.01$) in concentrations 50 and 100 mg/kg (Group 5 and 6) (122.63 and 111.93 mg/dl) respectively when compared with the CCl₄ treated group. Phytochemicals have always been an important source of remedies for human health problems. Numerous experimental and clinical studies have documented beneficial effects of phytotherapy for managing diabetes⁷. Antidiabetic effect of phytochemicals is mediated through different mechanisms such as decreasing glucose absorption from intestine, inhibiting glucose production in the liver, increasing glucose uptake by tissues, enhancing insulin secretion from beta cells, and/or increasing pancreatic tissue regeneration²⁸⁻³⁰.

The second method was the post-treatment, the results showed significant decrease ($p < 0.01$) in concentrations of serum blood glucose level (117.67 and 107.10 mg/dl) when treatment with methanolic extract 50 and 100 mg/kg (Group 7 and 8) respectively compared with the CCl₄ treated group. Furthermore, treatment with aqueous extract 50 and 100 mg/kg (Group 9 and 10) showed significant decrease ($p < 0.01$) in concentrations of serum blood glucose level (125.86 and 115.06 mg/dl) respectively when compared with the CCl₄ treated group.

Hundreds of plants that have been investigated for diabetes, a small fraction have shown the regenerative property, however, the number of studies supporting their beneficial effects on pancreas is not enough. Only *A. sativum*, *A. indica*, *berberine*, *C. sativus*, *G. sylvestre*, *J. regia*, *M. charantia*, and *N. sativa* had more than one piece of evidence for their regenerative property so that their consumption may decrease insulin dependence on diabetic patients. The antioxidant property of phytochemicals

may in part mediate their protective action against pancreatic beta cell apoptosis. Regardless of the molecular mechanisms, it seems that patients at the earliest stages of diabetes can be treated with these plants to delay or prevent the full destruction of pancreatic islets³¹.

AL-Azawi *et al.*,³² mention that peanut (*Arachis hypogaea* L.) skin extracts showed strong presence of phenolic compounds. Also, it exhibited strong antioxidant activity in the DPPH assays, and suggests the peanut skin extracts can be potentially used as a source of natural antioxidant agents. Peanut skins contain bioactive phenolic compounds including catechins and proanthocyanidins³³. The ability of the anthocyanins to induce insulin secretion is in the increasing order of pelargonidin-3-galactoside, cyanidin-3-glucoside, and delphinidin-3-glucoside. This finding demonstrates that the number of hydroxyl groups on the B-ring of anthocyanins plays a crucial role in their ability to secrete insulin³⁴. Some previous studies have shown that Tanacetum Parthenium Extract (TPE) has antidiabetic and antihyperglycemic effects²⁵. In assaying the effect of TPE on blood glucose, it was observed that CCl₄ injection significantly increases blood glucose level in damaged rats. In addition, administration of TPE in pretreatment groups prevented hyperglycemic effects of CCl₄.

Histopathological evaluation of peanut skin extracts on pancreas samples

The light microscopic examination obtained from the fragments of pancreas of the animals that were not exposed to CCl₄, but were given standard food (group 1) showed normal structure appearance of islet's cells of pancreas (Figure 1). The pancreas of CCl₄ intoxicated mice (group 2) showing fatty changes in the cells of islet and depletion of secretion (Figure 2).

Oxidative stress term is used to describe an imbalance between the systemic manifestation of free radicals and capability of cells to detoxify them and negate their damaging effects on proteins, lipid, and Deoxyribonucleic acid (DNA)³⁵. Some chemicals or drugs can cause liver and kidney damage such as carbon tetrachloride (CCl₄), acetaminophen and cisplatin³⁶. CCl₄ by itself does not have cytotoxic effects on the liver, but its metabolites CCl₃ and OOCCL₃ in hepatic parenchyma cells formed by cytochrome P450-dependent mono-oxygenases are responsible for the hepatotoxicity³⁷. The results of the present experiment are in agreement with Andritoiu *et al.*³⁸ demonstrates that the administration of CCl₄ leads to severe acute liver, spleen, pancreas in laboratory animals. In animals chronically exposed to CCl₄, unequal islets of Langerhans can be observed at the level of the pancreatic tissue, some of them hypertrophied, while in the peripancreatic adipose tissue, liponecrosis, is present.

The pre-treatment groups (group 3, 4, 5 and 6) in which the mice were administered with peanut skin extract orally for 35 days and injected (i.p.) 1.5 mg/kg of CCl₄ on the 35 day. The results showed glandular cells hypertrophy with few apoptotic cells changes when treated with 50 mg/kg methanolic extract of peanut (group 3) (Figure 3A), while in group 4 the result showed normal structure appearance of endocrine cells when treated with 100 mg/kg methanolic extract (Figure 3B). In group 5 treated with 50 mg/kg water extract showing high numbers of apoptotic cells changes of endocrine cells (Figure 3C), while in 100 mg/kg of peanut skin water extract (group 6) showed look like normal structure with rare apoptotic cells changes as shown in (Figure 3D). The post-treatment groups (group 7, 8, 9 and 10) in which the mice were injected (i.p.) 1.5 mg/kg of CCl₄ the 1st day and received peanut skin extract for 35 day. The results showed look like normal appearance but with congestion and apoptotic cells

changes when treated with 50 mg/kg methanolic extract of peanut (group 7) (Figure 4 A), However, in group 8 (treated with 100 mg/kg methanolic extract) the islet's of pancreas look like normal structure appearance (Figure 4 B). The histopathological section in the pancreas of mice treated with 50 mg/kg water extract (group 9) showing few apoptotic cells changes (Figure 4 C), while in 100 mg/kg of peanut skin water extract (group 10) the result showed look like normal structure appearance of islet's of langerhans as shown in (Figure 4 D).

Veghelyi *et al.*³⁹ mention that a single subcutaneous dose of carbon tetrachloride (CCl₄) in rodents was shown to cause lesions of chronic pancreatitis in advance of liver lesions, and which could be "altered at will" to yield a spectrum from the patchy lesions of chronic pancreatitis with or without concretions, through to 'pancreatic cirrhosis' or 'cystic fibrosis'.

Protection against oxidative damage caused by excessive reactive oxygen species (ROS) is essential for the health of tissues⁴⁰.

Khan *et al.*⁴¹ evaluated the methanol extract of *Launaea procumbens* (LPME) against carbon tetrachloride (CCl₄) induced pancreatic oxidative damage and hyperglycemia in mice and suggest that LPME effectively protects the liver and pancreas against the CCl₄ induced oxidative damage in rats, possibly through antioxidant and/or free radical scavenging effects of flavonoids and phenolic compounds in the extract. Some previous findings have indicated that the flavonoids substances in the plants have antioxidant and antidiabetic effects⁴². Considering the fact that many plants are rich with flavonoids and phenolic compounds, it seems that the observed effects are related to the return of antioxidant enzymes to normal levels or the prevention of severe damage to liver or pancreas⁴³. *Arachis hypogaea* skin extracts might exert its effects by preventing the destruction and maintains pancreas tissue via neutralizing ROS. The histopathological results demonstrated the benefit of peanut skin extracts on reducing the toxicity of CCl₄ in pancreas of laboratory animals.

Table 1: Phytochemical detection of *Arachis hypogaea* skin extracts

Phytochemical compound	Aqueous Extract	Methanolic Extract	Result
Flavonoids	+	+	yellow color
Phenols	ferric chloride	+	bluish green color
	lead acetate	+	reddish brown precipitate
Alkaloids	Wagner's test	+	reddish brown precipitate
	Meyer's test	+	White precipitate
Tannins	+	+	white gelatin
Glycosides	+	+	violet ring
Saponin	+	-	thick foam

(+) Positive, (-) negative.

Table 2: Acute toxicity and mortality rate of *Arachis hypogaea* skin extracts

Dose of extract mg/kg/ B.W	No. of mice per group	No. of dead / No. of animal	Sign of animal treated with extract
Aqueous extract			
100	6	0/6	Nil
250	6	0/6	Nil
500	6	0/6	Nil
1000	6	0/6	Tacky cardiac, increase breathing, sedation and animal tend to loneliness for one side in different time
2000	6	0/6	Tacky cardiac, increase breathing, sedation and animal tend to loneliness for one side in different time but it take long time than above
Methanolic extract			
100	6	0/6	Nil
250	6	0/6	Interrupted sedation
500	6	0/6	Tacky cardiac, shallow breathing and those signs are very clear
1000	6	0/6	Tacky cardiac, titanic hair skin, animal tend to loneliness for one side in different time
2000	6	0/6	Tacky cardiac, titanic hair skin, animal tend to loneliness for one side in different time all these signs take long time than above
Control			
1 ml/kg D.W	6	0/6	Nil

B.W = Body weight, D.W = Distil water

Table 3: Hodge and Sterner toxicity scale

No.	Term	Toxicity
1	Extremely Toxic	Less than 1 mg /kg
2	Highly Toxic	1 - 50 mg/ kg
3	Moderately Toxic	50 - 500 mg/ kg
4	Practically Non-Toxic	500 - 5000 mg /kg

Table 4: Effect of peanut skin extracts on blood glucose level

Groups	Glucose level (mg/dl)
Group 1	101.43 ± 2.02 e
Group 2	172.00 ± 2.08 a
Pre-treatment groups	
Group 3	112.60 ± 1.64 c
Group 4	104.27 ± 2.07 d
Group 5	122.63 ± 2.16 b
Group 6	111.93 ± 1.17 c
LSD value	5.833 **
Post-treatment groups	
Group 7	117.67 ± 0.92 c
Group 8	107.10 ± 1.75 d
Group 9	125.86 ± 1.12 b
Group 10	115.06 ± 1.77 c
LSD value	5.142 **

** (P<0.01). Means having with the different letters in same column differed significantly

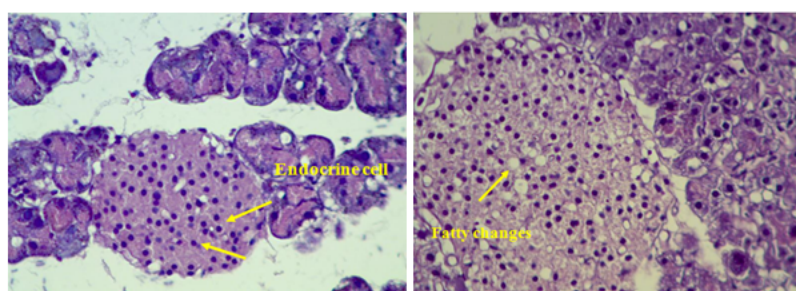


Figure (1): Normal structure appearance of islet's cells of pancreas (H&E stain 400 X).

Figure (2): Section showing fatty changes in the cells of islet and depletion of secretion (H&E stain 400 X).

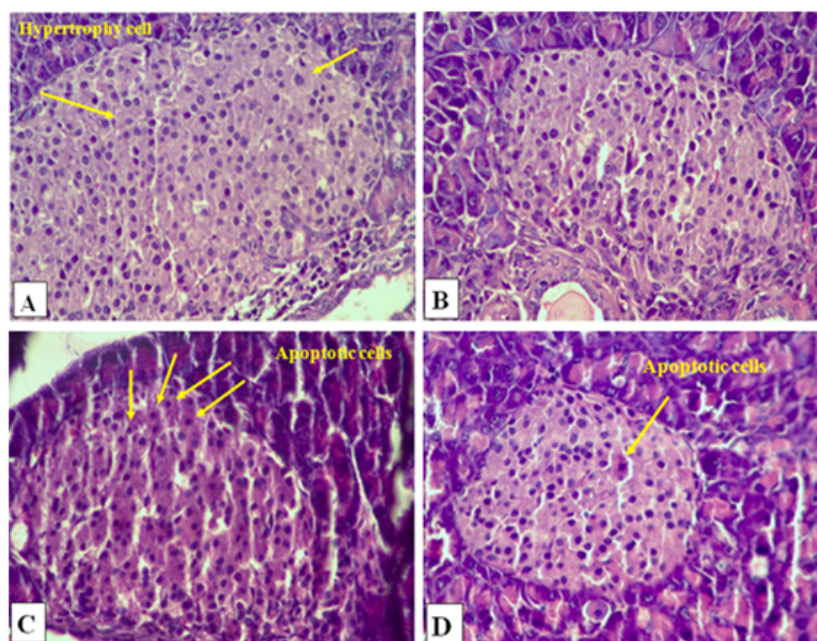


Figure (3): (A) Section showing glandular cells hypertrophy with few apoptotic cells changes; (B) Section showing normal structure appearance of endocrine cells; (C) Section showing high numbers of apoptotic cells changes of endocrine cells; (D) Section showing look like normal structure with rare apoptotic cells changes (H&E stain 400 X).

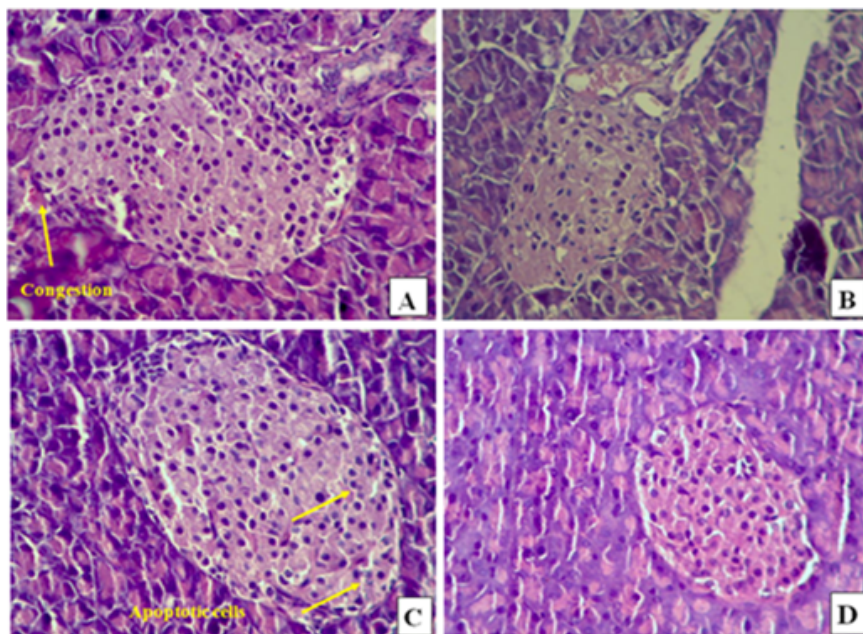


Figure (4): (A) Section showing look like normal appearance but with congestion and apoptotic cells changes; (B) Section showing the islet's of pancreas look like normal structure appearance; (C) Section showing few apoptotic cells changes; (D) Section showing look like normal structure appearance of islet's of langerhans (H&E stain 400 X).

Group 1: Control, **Group 2:** CCl₄ (3 ml/kg), **Group 3:** Methanolic extract (50 mg/kg) + CCl₄, **Group 4:** Methanolic extract (100 mg/kg) + CCl₄, **Group 5:** aqueous extract (50 mg/kg) + CCl₄, **Group 6:** aqueous extract (100 mg/kg) + CCl₄, **Group 7:** CCl₄ + Methanolic extract (50 mg/kg), **Group 8:** CCl₄ + Methanolic extract (100 mg/kg), **Group 9:** CCl₄ + aqueous extract (50 mg/kg), **Group 10:** CCl₄ + aqueous extract (100 mg/kg).

CONCLUSION

Arachis hypogaea skin extracts showed contains a number of phytochemicals. The phenolic compounds are the major components of these extracts and the antioxidant properties were attributed to them. The findings of this study showed that methanolic and aqueous extracts of *Arachis hypogaea* L. can protect pancreas and decrease the level of blood glucose for laboratory animals against damages induced by free radicals which are produced as the result of CCl₄ metabolism.

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