

Effect of Methanolic Extract of *Phoenix dactylifera L.* Seeds (PDS) on Blood Glucose levels of Normoglycemic and Dexamethasone induced Diabetic Rabbits

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Abstract

Background: The seeds of the date palm have also been shown to have nutritional and therapeutic properties. Plants are the source of many pharmaceutical compounds, so herbal treatments are attractive. In folk medicine, date seeds are commonly used to treat diabetes. Therefore, this study aimed to evaluate anti-diabetic potential of the methanolic extract of date palm seed (PDS) in dexamethasone (DMTZ) -induced diabetic rabbits.

Materials and Methods: The intraperitoneal injection of Dexamethasone (DMTZ) (150 mg/kg), experimental diabetes was induced in 42 male rabbits. The rabbits were divided into seven groups and administered the following treatments orally for 30 days: normal control (no treatment), placebo group, diabetic (no treatment), diabetic with PDS extract (200 mg/kg/day, P.O), diabetic with PDS extract (400 mg/kg/day, P.O), diabetic with PDS extract (400 mg/kg/day, P.O) with insulin (2UI/ kg B.Wt.), and diabetic with insulin (2UI/ kg B.Wt.). Histopathological examination of the pancreas was performed. The results are expressed as mean \pm SD and variations of some animals were compared in the using of one-way ANOVA. Statistical significance was set at $P \leq 0.05$. Statistical evaluation was performed using Microsoft Excel, and SPSS software version.

Results: The methanolic PDS extract has been shown to have a significant anti-diabetic effect ($P \leq 0.05$). This effect may be due to the presence of flavonoids, saponins and fatty acids in the extract, which could function through different mechanisms. Furthermore, pancreas tissue regeneration was histologically clean. However, further research is needed to isolate and elucidate the bioactive compound(s) responsible for its anti-diabetic properties, as well as its molecular mechanism of action.

Conclusion: This study suggests the anti-diabetic potential of date palm seed extract, which might be due to its hypoglycemic properties.

1. Introduction

Phoenix is the surname of seventeen palm species (*canariensis*, *dactylifera*, *reclinata*, *sabal*, *rupicola*. . .etc.) which a member of the palmate family¹. For many people living in Yemen and other dry areas of the world, the feather palm (*Phoenix dactylifera L.*) plays a significant social, environmental, and economic role. The fruits of the feather palm are widely consumed in many parts of the world and are considered a major part of the diet and a staple food in most Arab countries, The seeds of *Phoenix dactylifera L.* (Arecaceae) have been found to contain a wide range of inhibitors.² Many studies have examined the chemical composition of *P. dactylifera* seeds, revealing the existence of large amounts of phenolics, flavonoids, and amino acids, all of which are responsible for radical scavenging and medicinal operation^{3,4,5}. According to a recent phytochemical study, the flavonoid content in *P. dactylifera* seeds is rutin and quercetin and, which are increased by preparation.⁶ *Phoenix dactylifera L.* (date palm) is a plant used in folk medicine to treat a variety of diseases and disorders, Dates and its constituents act as potent inhibitors, medicinal drugs, and antitumoral agents and provide an appropriate variety of medical aids in the treatment of various diseases.⁷

Diabetes may be a significant pathological condition, affects one-fifth of the world's population. Diabetes mellitus is a multi-etiological condition characterized by chronic symptoms,⁸ due to insufficient insulin hormone production or cells that do not respond to the hormones produced⁹. It is a condition in which the body produces insufficient insulin, stops producing insulin, or becomes increasingly resistant to its activity¹⁰. In patients with the polygenic condition, effective glucose control is the key to preventing diabetic complications and improving quality of life.^{2,7} The ability of insulin hormone to mediate tissue glucose uptake may be a critical step in preserving the physiological state of glucose and clearing the postprandial glucose load.^{11,12} In 2019, 463 million people worldwide have diabetes, accounting for 9.3% of the global population, with 80% of those living in low and middle-income nations. According to estimates, 2045, 700 million people will make up 10.9 percent of the global population.^{13,14}

Diabetes mellitus can cause symptoms such as thirst, polyuria, blurred vision, and weight loss. Several pathogenic processes are involved in the development of polygenic disorders. With sequential hormone deficiency, represents processes that destroy pancreatic beta cells. Abnormalities in sugar, fat, and macromolecule metabolism are caused by a lack of hormone action on course tissues as a result of hormone inability or lack.⁸

For a long time, diabetes has been treated using a variety of medicinal plants, with medicinal plant extracts being reported to improve diabetic control while reducing related adverse effects when compared to synthetic medications.¹⁵

Dexamethasone is a sex hormone. Steroids increase glucose levels in three ways: they block the action of insulin, which causes hormone resistance, and less glucose is ready to move out of the blood to be concerned by the muscles. This causes the liver to release additional glucose into the blood, resulting in a high glucose level¹⁶. Dexamethasone use utilize to improve analgesia and reduce the incidence of nausea and vomiting. Dexamethasone, on the other hand, has the potential to raise blood glucose levels, which is a known risk factor for problems¹⁷. The hypoglycemic effects of various components of various palm species have been reported in some studies.

In a recent study, the liquid extract of *P. dactylifera* L. seeds was found to be capable of stimulating endogenous hormone secretion through additional sources, which may be the mechanism of its hypoglycemic action.¹¹ Another study found that a fruit extract of *P. dactylifera* has a protective effect against diabetic pathology in rats¹². Many indigenous medicinal herbs and extracts from various sections of these plants such as roots, shoots, and seeds. have been used in the management of diabetes¹⁸ due of the different active phytochemicals present in these plants.

However, the goal of this research was to assess the possibility of using the date palm seed as an anti-diabetic agent in non-diabetic and diabetic rabbits induced by dexamethasone; the Methanolic extract of the seed had a hypoglycemic effect.

2. Materials & Methods

2.1 Plant material

The seeds were obtained from Albalh Dates collected in Tehama / Alhodidah, Yemen, from the fruits of Phoenix dactylifera L. (Arecaceae), The plant was identified by Dr. Zamila Ahmed, Demonstrator at the Faculty of Science Department of Plants, Sana'a University, Sana'a, Yemen. The seeds were sun-dried before being roasted at 40% and then ground to a fine powder by gender.

2.2. Preparation of methanolic crude extract (whole product)

2.2.1. Maceration

The seeds of PDS were collected from Tehama in Yemen

30 kilograms of Phoenix dactylifera L. fruit were removed from the seeds and washed thoroughly with distilled water before being dried by the sun and roasted in an oven (Memmert, Model; SFE600, Schwabach, Germany), at 40-50 C for 4 h. They were then pulverized into a fine powder using a grinder (Taizhou Jincheng Pharmaceutical Machinery Co., Ltd., Model; SF, Jiangsu, China), and soaked in 99.9% methanol (W/V) at room temperature (25C°) for 4 weeks and shaken several times with shaker equipment (GFL 3017 Shaker, Serial No. 103488051, Germany), (maceration method). The extract-containing methanol was filtered with gauze followed by Whatman filter (Whatman, Buckinghamshire, England), and the residue was combined with methanol at a ratio of (W/V). The filtrate was vacuum distilled at 40 °C in a rotary evaporator (Buchi rotavapour R-200 equipped with buchi heating bath B-490, buchi vacuum controller V-800, Germany). The final extract was a red semi-solid with a dry weight of 90% weighed by balance (Electronic balance, APEX-100, Denver instrument, Germany). This methanol extract (as a whole product).¹⁹

2.2.2. Fractionation

The overall semi-solid of the complete product of the methanolic extract was placed in a separating funnel, shaken, and allowed to stand for minutes before collecting the benzene layer in an excess beaker. When using 250 cc of aromatic hydrocarbons, the procedure repeated twice. Starting with Hexane, pet. Ether, chloroform, Ethyl acetate, and distal water, the previous step was repeated with entirely different solvents wherever possible. On 9 extracts the following fraction was obtained: (Benzene; Hexane; pet. Ether; chloroform; oily; emulsion; ethyl acetate; aqueous; and methanol).

2.2.3. Preliminary phytochemical screening

A preliminary phytochemical analysis of the plant extract was carried out by using Thin Layer Chromatography (T.L.C) plates coated with silica gel 60 F254 for T.L.C. The mobile phase Ethyl acetate: Methanol (9.5:0.5) was added to the chromatotank and left for a time to saturate the tank; micro-drops of the concentrated solutions of the fractions obtained (benzene, hexane, petroleum ether, chloroform, oily, emulsion, ethyl acetate, aqueous and methanol extracts) were spotted on pre-coated Silica gel. The chromatogram after complete development was air dried and visualized with different chemical reagents.

2.3. Experimental animals

Male rabbits weighing 0.77-1.5 kg are healthy. They were collected from the animal house of the Faculty of Science, Sana'a University. The Animal Ethics committee, Government of Yemen constituted, Sana'a University, accepted the current study before the start of the experiment. The animals were held in standard polypropylene cages with a 12:12 hour light/dark cycle and under controlled temperature (25 ± 2 °C) and kept at the same room temperature and humidity. Before beginning the experiment, all the rabbits were given a 14-day acclimatization period.

2.4. Acute toxicity study

Male rabbits randomly divided into three groups of three rabbit per group. Group one was the untreated control rabbit. Group two was given 1-2 ml of distilled water, which was used as a placebo control. Group three included rabbits treated with a single oral dose of 5,000 mg/kg extract. Acute toxicity testing according to the Organization for Economic Cooperation and Development's (OECD) updated up-and-down protocol²¹. Before the start of the experiment, rabbits were fasted from food but not water for the night before the extract was given orally. Based on the individual animal body weights obtained on the day of dosing of the acute toxicity study doses (1,000, 2,000, 3,000, 4,000, to 5,000 mg/kg b.w.), was dissolved in distilled water at an administration volume of 10 ml/kg body weight and given to the first rabbit by oral gavage, then hourly for 3 hours, and finally regularly until 48 hours. For 14 days, all the experimental animals were kept under close observation, and the number of rabbits that did not die during the study period was recorded. Toxicity in the short term, no mortality was observed at the end of the experiment after a single dose oral administration of PDS extract to rabbits up to a dose of (5,000 mg/kg).

2.5. Induction of diabetes

A single dose of dexamethasone (150 mg/kg) was administered intraperitoneally to induce diabetes.²² Male rabbits fasted an 18-hour. Blood from the rabbits' hearts was used to assess their fasting blood sugar (FBS) levels before being injected with dexamethasone. To induce hyperglycemia, freshly prepared dexamethasone was dissolved in normal saline (0.9% w/v NaCl) and injected intraperitoneally as a single dose of 150 mg/kg. Rabbits were held on 5% glucose for the next 24 hours to prevent fatal hypoglycemia caused by major pancreatic insulin release.²² Rabbits with a fasting blood glucose level of more than 250 mg/DL after 72 hours were considered as diabetic. The experiment was approved by the Institutional Ethical Committee, Faculty of Pharmacy, Sana'a University.

2.6. Experimental design Evaluation of Antidiabetic activity of PDS methanolic extract in dexamethasone-induced diabetic

Rabbits divided into two major groups as shown in Diagram No (A-1). After 72 hours from the administration of dexamethasone to rabbits with hyperglycemia, more than 250 mg/dl was selected and is used for the experiment. The rabbits were administered the extract (dissolved in normal saline from 1-2 ml) for two weeks orally by using a feeding cannula. For the experimental rabbits, FBG was estimated before the start of treatment, on one week and two weeks, and 30 days of treatment. All rabbits were later sacrificed on 30th days by diethyl ether and the Pancreases were collected in 20% formalin for histopathological examination.

2.7. Histopathological examination of Pancreas

For the histological study, specimens of pancreases were immersed in neutral buffered formalin (10%) for 48 hours. A routine method of dehydration in ascending series of ethanol, followed by tissue clearing using, clearing with xylene and embedding in paraffin was used. Sections of 5- μ m thickness were sliced using a microtome and were stained with Hematoxylin and Eosin stain²³.

2.8. Histopathological studies

Tissue samples of the pancreas were fixed in 10% buffered formalin and were processed for histopathological examination. A routine method of dehydration in ascending series of ethanol, clearing with xylene, and embedding in paraffin was used. Sections of

5- μ m thickness were sliced using a microtome and were stained with Hematoxylin and Eosin stain.²³

2.9. Statistical analysis

The results were expressed as mean \pm SD and differences among the groups of animals were compared using one-way ANOVA with posthoc LSD's test. Statistical significance was set at $P \leq 0.05$. Statistical analysis was performed using Microsoft Excel, and SPSS software version.

3. Results

3.1. Phytochemical analysis and acute toxicity assessment

A phytochemical screening of the PDS (Table. 1) revealed the existence of steroids, amino acids, lipids, fatty acids, flavonoids, phenols, anthraquinone and saponins., were abundant in the extract.

Acute toxicity test results

Physical and behavioral tests were used to determine the acute toxicity of a methanolic extract (crude product) of *Phoenix dactylifera* L. seeds. During the 14-day observation period, administration of the extract with a single oral dose of 5000mg/kg did not result in mortality. During the experiment, no general behavior, physiological activities, or signs of toxicity were observed, such as changes in the color of the eyes, and urine, abnormal secretion, nausea, diarrhea, sleep, or hair erection.

3.2. Hypoglycemic activity of PDS in non-diabetic rabbits

The extract at 200 mg/kg showed significant hypoglycemic activity in non-induced hyperglycemic rabbits ($P < 0.05$), with groups (3,4,5,6) with the extracts of the whole product, aqueous, methanol, and emulsion showing a decrease in blood glucose and with oily extract group (7) showing an increase in blood glucose in non-diabetic rabbits, as shown in Table (2).

3.3. Hypoglycemic activity of PDS and its extracts upon subacute administration in dexamethasone-induced diabetic rabbits

As shown in the FIG. (1): The methanol extract of PDS has hypoglycemic activity in dexamethasone-induced diabetic rabbits when given subacutely. Methanol extract at 200 mg/kg had a significant antidiabetic effect from the 1st week onwards ($P < 0.05$) fig (c). And Methanol extract at 400 mg/kg had a significant antidiabetic effect from the 2nd week onwards ($P < 0.05$), fig (D). Nevertheless, the administration of the extract at 200 mg/kg had an antidiabetic effect. In diabetic rabbits, dose-dependent antidiabetic activity experiments revealed that the extract had a remarkable hypoglycemic effect at 400 mg/kg ($P < 0.05$). As shown in Table (3). Methanol extract in two doses, 200 mg/kg and 400 mg/kg had a hypoglycemic effect ($P < 0.05$), at 400 mg/kg being the most effective in lowering glucose levels (Table 3) Figure (C, D). Administration of insulin at 2UI/kg had an anti-diabetic effect in fig(E); however, when insulin 2UI/kg was combined with methanol extract 400 mg/kg, there was a greater reduction in blood sugar as shown in fig(F).

4. Discussion

The anti-diabetic potential of *P. dactylifera* seeds PDS extract were evaluated by assessing its hypoglycemic activity in dexamethasone-induced diabetic rabbits. In the present study, treatment with PDS and its extracts had a significant antihyperglycaemic effect. The phytochemical and nutritional contents of the PDS have the most abundant fatty acids in date seed oils, were oleic, lauric, myristic, palmitic, and linoleic acids. Date seeds had phenolic and flavonoid content, saponin, steroids, amino acids, phenols respectively. Date seeds could be employed as components to boost the nutritional value of various functional foods for human consumption, as well as used as food, medicinal, and cosmetic additives, according to the findings^{24,25}. The acute toxicity of the substance was investigated up to a high concentration of 5,000 mg/kg b.w. (20 times more than the therapeutic dose), The extract showed no signs of toxicity even at this level. The main goal of preliminary acute toxicity research is to get a sense of whether there would be noticeable behavioral abnormalities or mortality, and PDS did not show any toxic signs in this limited toxicity test in male rabbits. According to a survey of the literature, no studies on this plant's other pharmacological qualities or phytochemistry have been conducted. Dexamethasone are known to increase blood glucose levels by stimulating hepatic gluconeogenesis and increasing insulin resistance^{22,26}. In animal investigations, Dexamethasone administration has been shown to

cause insulin resistance and hyperglycemia. When the dose of dexamethasone 150 mg/kg was given, the hyperglycemic impact of Dexamethasone was potentiated/aggravated, according to our findings²⁷. Dexamethasone can produce rise in blood glucose levels by stimulating hepatic gluconeogenesis and increasing insulin resistance.¹⁷

They also stimulate the liver to release additional glucose into the bloodstream. Although date palm seeds *PDS* have long been used in traditional medicine to treat diabetes, few studies have looked at their anti-diabetic properties. Previous research has shown that when paired with insulin, the aq *PDS* improves glycemic control in diabetic rats compared to insulin alone, and this effect could be attributed to the stimulation of insulin production¹¹.

The hypoglycemic effect of *Phoenix dactylifera L* seeds extracts may be due to one or more of the following mechanisms: -

- 1. It may be able to imitate the actions of insulin** may have a mode of action similar to hypoglycemic insulin, which promotes insulin production by closing K⁺-ATP (adenosine 5-triphosphate) channels. This causes membrane depolarization and an increase in Ca²⁺ influx, and it is an important first step in insulin secretion.
- 2. Normal beta-cell function for glucose-fatty acid cross-talk in insulin secretion control** to induce insulin production, glucose must first enter the beta cell via a glucose transporter and then be digested to a level higher than pyruvate in a process started by the high enzyme glucokinase. This, in turn, is hypothesized to result in an increase in the ATP:ADP ratio as show in diagram (1), cell depolarization, and opening of the voltage-sensitive Ca²⁺ channels, resulting in an increase in intracellular [Ca²⁺] and activation of exocytosis. Additional pathways, on the other hand, contribute to insulin secretion regulation throughout the whole animal. The K⁺ ATP channel-independent pathway, for example, enhances the response to a higher [Ca²⁺] generated by the more traditional method. A second mechanism of glucose signaling, known as the K⁺ ATP channel-independent, Ca²⁺-independent pathway, appears to entail a GTP-dependent step that is activated by the combined activities of protein kinase A (PKA) and protein kinase C. (PKC).²⁸ Several additional plants have been shown to have antihyperglycaemic and insulin-stimulatory properties in this setting.
- 3. Tissue sensitivity to available nutrients has increased.** further, this antidiabetic activity indicates that *Phoenix dactylifera L.* may stimulate insulin secretion from the remaining β -cells or regenerated β -cells this effect may be due to the effect of saponin which exerts its hypoglycemic effect, which exerts its hypoglycemic effect. An extra-pancreatic mechanism includes increased insulin-receptorbinding, and increases transmembrane passage of glucose across cells membranes of most body cell, which promotes the conversion of glucose to glycogen through induction of glucokinase and glycogen synthase²⁹.
- 4. It may be due to the effect of active fatty and amino acids, flavonoids, phenols, and steroids;** these compounds may scavenge free radicals liberated by dexamethasone in diabetic rabbits²⁷. **Insulin** is involved in the metabolism of lipids as well as the regulation of carbohydrate metabolism. Insulin reduces the activity of hormone-sensitive lipases in adipose tissue and reduces the release of free fatty acids, making it a strong lipolysis inhibitor. This enzyme's activity is increased in diabetes, which enhances lipolysis and releases more free fatty acids into circulation. The extract and its components appear to exhibit insulin-like activity, according to our findings. In diabetics, higher fatty acid concentrations increased fatty acid -oxidation, resulting in more acetyl-CoA and cholesterol. Some plants with flavonoids and fatty acids, as well as steroids, have been shown to have hypoglycemic effects.^{30,31} The mechanism of action of the PDS extract's anti-diabetic activities is unknown. However, phytochemical elements such as flavonoids, fatty, and amino acids, tannins, steroids, and others are likely to be returned. These compounds are derived from a variety of plant sources and be effective hypoglycemic agents³². Numerous studies have found flavonoids to have anti-diabetic, anti-hyperlipidemic, and antioxidant properties^{33,34,35}. **Flavonoids** can lower blood glucose levels through both pancreatic and extra pancreatic pathways. In vitro and in vivo systems, they can serve as insulin secretagogues, increasing insulin secretion^{36,37}. They can also lower glucose absorption by inhibiting -glucosidase activity in the intestine³⁸. The presence **of fatty acids** in the seeds may play a role in lowering blood sugar levels by inducing insulin release from pancreatic cells, as show in the diagram no. (1). Diabetes, a disease in which glucose and lipid metabolism are inadequately regulated by insulin, is a severe global health issue^{8,9}. Insulin is released by pancreatic cells in response to high blood glucose levels, and its release is influenced by a variety of factors¹³. Free fatty acids (FFAs) are a significant source of energy as well as signaling molecules in a variety of physiological functions, including insulin secretion^{39,40}. Increased levels of free fatty acids [FFA] have been associated to insulin resistance and cell malfunction. However, believing that decreased glucose absorption in muscle is attributable to increased fatty acid oxidation and decreased glucose oxidation²⁷. FFAs are thought to enhance insulin secretion in the short term. This mechanism, however, is not well-understood². GPR40, a G-protein-coupled

receptor abundantly expressed in the pancreas, is shown to operate as a receptor for long-chain FFAs. Furthermore, we show that long-chain FFAs activate GPR40, which increases glucose-stimulated insulin release from pancreatic cells.^{41,42} The presence of glucose activates an enzyme, which transforms glucose into a molecule that plays a vital part in the secretion of insulin, as illustrated in the picture that shows diagram no. (1), how insulin is produced in the presence of glucose, amino acids, flavonoids, and fatty acids. The chemical acetylcholine, on the other hand, plays a critical function in blocking fatty acid oxidation and aids in increasing fatty acid production, which promotes insulin secretion. While the chemical stimulates beta receptors in pancreatic cells, increasing insulin secretion, it also inhibits alpha receptors, lowering fatty acid oxidation and increasing insulin secretion as shown in the diagram no.(1).²⁸

5. Anti-diabetic medications that could be developed in the future, Alpha antagonists. In the development of highly specific antagonists for the treatment of type 2 diabetes (inhibition of insulin production via the 2-receptor), Fatty acid oxidation is inhibited by an antagonist of the alpha 2-receptor and activator of glucokinase. Alpha antagonists, which are potential novel anti-diabetic medicines, have a limited therapeutic utility. The development of highly specific antagonists for the treatment of type 2 diabetes, because normal adrenaline-driven glucose release from the liver is reduced and controlled by B-receptors, the use of B-receptor antagonists worsens the caused hypoglycemia in diabetes patients. A number of medicines are now being investigated, including alpha 2 adrenoceptor antagonists and glucokinase activators. Because B3 adrenoceptors control lipolysis in fat cells, researchers are looking into the idea of utilizing selective B3 agonists, which are currently under development for the treatment of obesity and type 2 diabetes.^{43, 44}

Methanol PDS treatment of diabetic rabbits resulted in a considerable improvement in the diabetic group. This impact could be explained by the good glycemic control provided by methanol extract of PDS, as evidenced by the large reduction (by 80%) in blood glucose levels compared to the diabetics' fig (C, D) who were not treated in fig (B). In histopathology, the degeneration observed in the pancreas of dexamethasone-induced diabetic rabbits may be due to the necrotic action of dexamethasone on the beta cells fig (B)⁴⁵. The degenerative changes induced by dexamethasone in rabbit's pancreas were recovered by PDS extract and insulin fig (E) which was followed by regeneration of the islet cells and increased tissue density with attendant improved insulin production and reduction of FBG in rabbits. This effect was more pronounced at 400 mg/kg PDS extract fig (D). It has been demonstrated that beta cells can regenerate from stem cells located in pancreatic ducts or from progenitor cells residing inside islets⁴⁶. Regeneration of the islet cells by PDS extract may involve the promotion of the above mechanisms. In addition, fatty acids, flavonoids are reported to regenerate the damaged pancreatic β -cells in diabetics. As a result, the presence of fatty acids, amino acids and flavonoids in *P. dactylifera* seeds may explain our findings of the antihyperglycemic effects in the diabetic rabbits induced by dexamethasone.

5. Conclusion

PDS and its extracts have a hypoglycemic impact in dexamethasone-induced diabetic rabbits, according to the findings of the current study. PDS and its extracts may have anti-diabetic benefits by increasing insulin secretion, stimulating glucose uptake and glycogen synthesis in cells, and/or protecting pancreatic β -cells from dexamethasone- and glucose-induced oxidative stress. The presence of flavonoids and fatty acids in the methanol extract may cause this action, which is dose and duration-dependent. They operate through a variety of techniques. However, more research is needed to isolate and understand the bioactive compound(s) responsible for the antihyperglycemic effect, as well as the molecular mechanism of action. As a result, *Phoenix dactylifera L.* seed's extract could be used as a supplement to insulin in order to extend the duration of action, improve the efficacy, and/or reduce the doses, lowering the risk of side effects.

Declarations

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Tables

Tables 1 - 3 are available in the supplementary files section.

Figures

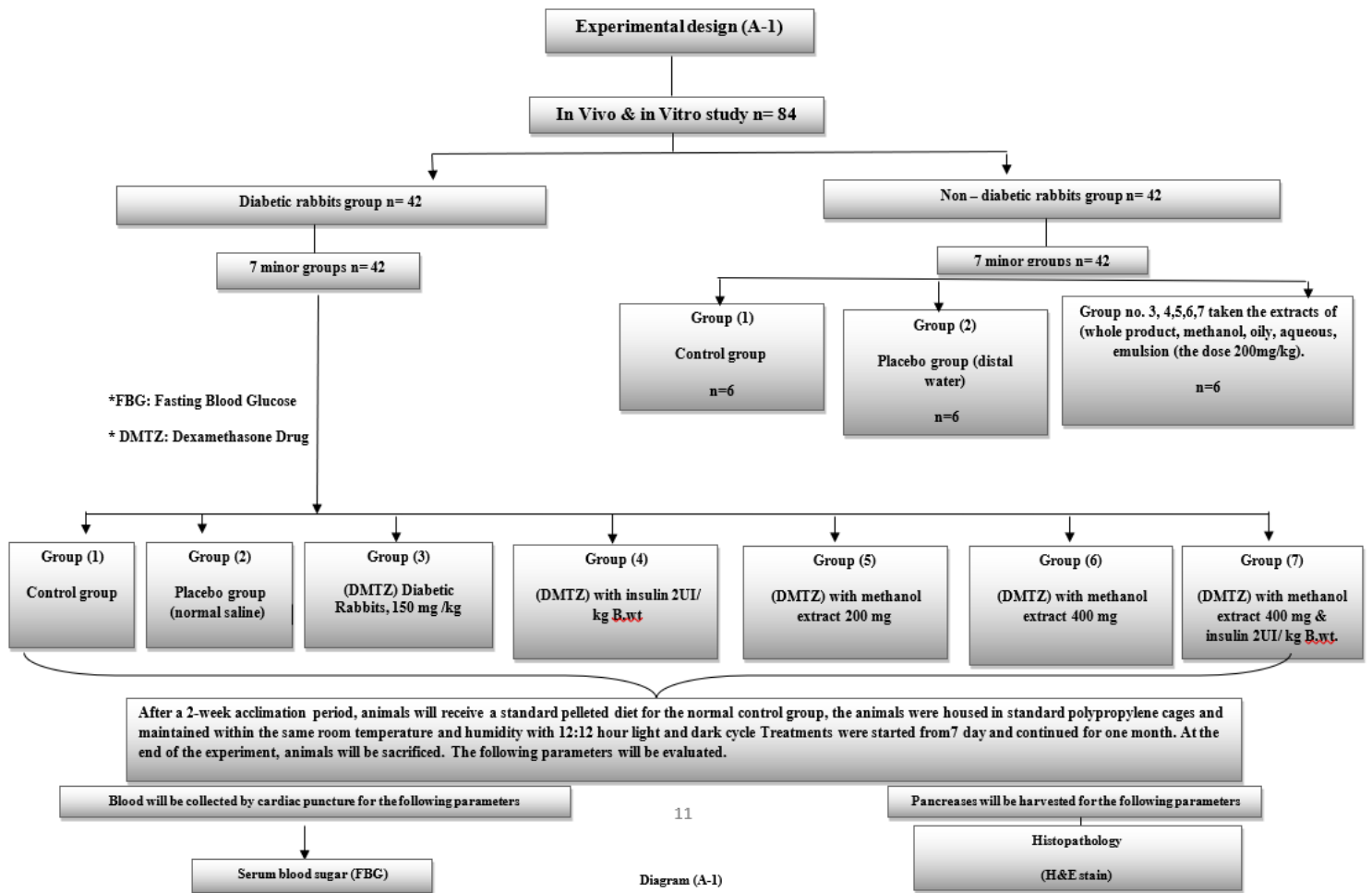


Figure 1

Diagram A-1. Legend not available with this version.

Figure 2

Diagram 1. Legend not available with this version.



Figure 3

Figure 1 legend not available with this version.

Supplementary Files

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