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EFFECT OF PLUM FRUIT EXTRACT *(PRUNUS DOMESTICA L.)* ON HEPAR HISTOLOGY IN MALE WISTAR RATS (RATTUS NORVEGICUS) FOLLOWING ALLOXAN INDUCTION

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ABSTRACT

Background: Hyperglycemia is when blood glucose levels are above normal ranges. Having high blood sugar might cause problems with the organs. Chemical medications have adverse effects like hypoglycemia and liver harm but can lower glucose levels over normal limits. The public requires safe alternative therapies with few adverse effects. Flavonoids in plums can raise adiponectin levels, which are crucial for controlling blood glucose levels. Because there is little information on the impact of plums on hyperglycemia, researchers are interested in performing this study. **Objective:** Examining the impact that administering plum (Prunus domestica L) extract had on the hepar histopathology of male Wistar rats (Rattus norvegicus) that had been induced to become hyperglycemic through the use of Alloxan. **Method:** Experimental research with a posttest-only control group design is being conducted. 35 Wistar rats were placed into five groups, each receiving oral doses of 100, 200, or 300 mg/kg B.W./day of plum extract: the healthy control group (C1), the negative control group (C2), and the treatment groups (T1-3). Furthermore, C1 was given food and drank at will, while C2 and T1-3 were induced via an intraperitoneal alloxan injection. On days 0 through 14, blood sugar levels were assessed on those days. The Wistar was stopped on the 28th day, and hepar tissue preparation and hematoxylin-eosin staining were performed. Observations were made using a 100x or 400x magnification in a microscope. Mordue scores were used to evaluate abnormality on hepar. **Result:** In comparison to dosages of 100 mg/kg B.W./day and 200 mg/kg B.W./day, blood sugar levels and abnormality rates in the rat group receiving the plum extract at a dose of 300 mg/kg B.W./day were lower. The T2-T3 group differed significantly from the T1 or C2 groups. No difference between the T2 and T3 groups is notable. **Conclusion:** The significant differences between the groups that received plum extract along with Alloxan (T1-3) and the group that received Alloxan alone show that the administration of plum extract can lower blood sugar levels and abnormality in hepar rats.

***Keywords**: hyperglycemia, plum, histology, hepar, Necrosis*

BACKGROUND

An efficient management method is crucial because diabetes mellitus (D.M.) is one of many nations' top causes of death. High blood glucose levels and anomalies in the metabolism of carbohydrates, proteins, and fats are the defining features of this metabolic illness[1]. Alternative remedies for D.M. are still being pursued because of the shortcomings of existing therapy. It is frequently stated that increasing dietary fiber intake may improve the management and control of diabetes, cancer, and cardiovascular illnesses[2].

Between 80 and ninety percent of the fruit's overall weight is water. Fruit peel consists of a full-size amount of insoluble fiber, while fruit flesh has a large quantity of soluble fiber. On the side of veggies, culmination are meals excessive in fiber. Fruits incorporate beta-carotene, folate, nutrients B, C, and E, and minerals like magnesium and potassium. Culmination hardly ever includes saturated fatty acids, LDL cholesterol, fat, or salt[3].

Fruits are noted for having low energy density and being incredibly satiating due to their high fiber and water content. They are also regarded as being nutritious. Beta-carotene, phytochemicals, and vitamins C and E are examples of nutrients that have antioxidant properties. Fruits can take the place of calorie-dense snacks since they are typically eaten fresh as a dessert or a snack[4].

The fleshy fruits of various Prunus species, including P. Domestica, P. salicina, and P. Americana, include plums. More than 100 species of plums have been cultivated in temperate zones worldwide since the dawn of time. Dried plums are frequently referred to as prunes. Small to medium-sized plants include trees. The leaves are elliptic or oval, with short petioles, sharp or obtuse ends, and crenulate edges. Usually, two to three small, white

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blooms with extended pedicels are born in umbel-like clusters on short spurs. One-year-old wood's axils can also be found alone, in pairs, or small groups of two to three. Fruits have a glorious surface and are fleshy, oblong, round, or conical. Fruits come in a range of colours and sizes[5].

Minerals, vitamins (A, B1, B2, B3, B5, B6, C, and folate), fibre, and carbohydrates are all abundant in plums (calcium, magnesium, zinc, copper, selenium, potassium, and iron). Furthermore, they have very few calories and fat. The fruits' high moisture content makes them more susceptible to physical, chemical, and microbiological harm, which may also be why they have a short shelf life[6]. In addition to their nutritional value, Prunus species have high concentrations of bioactive dietary components such as phytosterols (d-sitosterol and stigmasterol), fatty acids (oleic acid, linoleic acid, palmitic acid, and stearic acid), and polyphenols (phenolic acids, flavonols, and flavan-3-ols)[7].

The fruit of this plant is used in various ways, including as food, a laxative, a digestive aid, and for its advantageous hypotensive, hypoglycemic, and hepatoprotective properties[8]. The biological activity of plums has primarily been attributed to their high phenolic chemical content[9]. Phenols occur in plants as free (free phenols that can be extracted with a variety of solvents) or secondary (bound to cell wall proteins or polysaccharides to form stable insoluble complexes) in plants. Chemicals. Standard methods of hydrolysis include acid-base or enzymatic methods that release the bound phenol[9]. Studies on bound phenolics are uncommon in current literature, which focuses more on free phenolics' structure and biological actions. Vegetables, fruits, and legumes/seeds can bond phenols to a relatively high percentage (20%–60%)[10]. Furthermore, it has been shown that bound phenolics have strong biological effects, including anti-inflammatory, probiotic, anti-obesity, antioxidant, and therapeutic effects on CNS diseases[11].

Plums have terpenoids and flavonoids that help raise adiponectin, a hormone crucial for controlling blood sugar levels[1]. Plum fruits are a significant energy source from simple sugars. Still, they do not cause a significant rise in blood sugar levels, probably because of their high fiber, fructose, and sorbitol content[8]. In addition plums contain large amounts of phenolic compounds especially chlorogenic and chlorogenic acids which can contribute to the laxative effect and delay the absorption of glucose. Anthocyanins and flavonoids are mainly concentrated in the skin of the fruit and have strong anti-inflammatory antioxidant anti-carcinogenic and anti-diabetic properties. Thus it plays an important role in the prevention of cardiovascular disease and neuroprotective function[12]. The presence of polyphenols in the plant is associated with the antioxidant and anti-inflammatory properties of the extract. Metabolic dysregulation and oxidative stress greatly influence the pathophysiology of DM. Antioxidant-rich plant extracts help treat diabetes[13].

According to a previous study, P. Domestica fruit extract decreased the enzyme activities of -amylase, -glucosidase, pancreatic lipase, and HMG CoA reductase, with IC50 values of 7.01 mg/mL, 6.4 mg/mL, 6.0 mg/mL, and 2.5 mg/mL, respectively. The amount of nitrite, interleukin-1, and PGE2 produced by lipopolysaccharide-activated J774 macrophages was decreased by P. Domestica fruit extract. According to the study's findings, P. Domestica fruit extracts have a positive modulatory effect in vitro on several molecular processes linked to the pathophysiology of cardiometabolic diseases[6]. Researchers are interested in doing this study since there has been little research on the influence of fruit plums on hyperglycemia.

METHOD

The type of experimental research used in this study was a post-test group design using only male Wistar rats (Ratus norwegian) as the research model. Thirty-five Wistar rats were divided into five groups each consisting of seven continents that were randomly selected and two reserves. On day 0 blood was collected from each mouse and their fasting blood glucose levels were determined. Aquatest was given to the negative control group (C1). An intraperitoneal injection of 150 mg/kg BW Alloxan was used to treat the positive activity group (C2). Tomorrow blood glucose level 2 on the third day of fasting. Treatment is continued if the blood sugar level exceeds 200 mg/dl. Deduction of 14 days of treatment. In the treatment of Groups T 1 and 2 each plum extract 100 mg/kg BW/day plum 200 mg/kg BW/day and plum extract 300 mg/kg BW/day. 1 (T1). Treatment group 3 (T3) also received grain

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extract 300 mg/kg BW/day orally. Mice are given blood samples on days 7 and 14 to measure fasting blood glucose 3 and 4.

The rats were terminated for each treatment group on the fourteenth day, after which they were dissected and prepared in preparation blocks. The preparation block holding the tissue is adhered to the object's glass using albumin, then placed in a water bath and let stand for a while. Continue with the Hematoxylin-Eosin coloring after the preparation block is finished. To determine whether the organ had any damage or Necrosis, observations were made under a microscope at 100x and 400x. A Mordue score was used to assess the findings.

Score 0	No degeneration or Necrosis found
Score 1	Degeneration and Necrosis found in 1-20 % of fields of view
Score 2	Degeneration and Necrosis found in 21-50 % of fields of view
Score 3	Degeneration and Necrosis found in 51-75 % of fields of view
Score 4	Degeneration and Necrosis found in > 75 % of fields of view

Figure 1. Mordue Score[9]

The data from the sample group were processed using the SPSS 17 computer program. Due to the small number of samples, a distribution normality test using the Shapiro-Wilk test was performed. Because the data were not normally distributed, the Kruskal Wallis non-parametric test was followed by the Mann-Whitney post hoc test. If the p-value was less than 0.05, the difference was considered meaningful.

RESULT

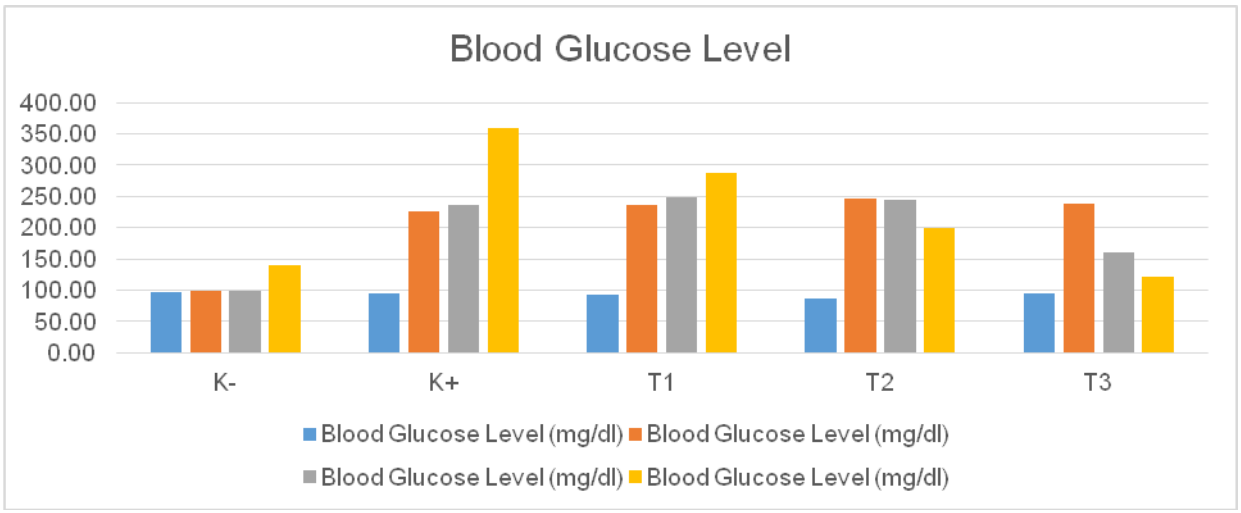

Figure 2. Blood glucose level

The negative control group (C1) was significantly different from the positive group (C2) at T1 and T2. This means that there is a significant difference in blood sugar levels. Negative control group (C1) received no alloxan-containing plum extract or treatment group 3 received plum extract 300 mg/kg B.W. After one day of alloxa there was little difference compared to the other treatment groups. This means that the blood sugar readings are about the same or slightly different. Alloxan (T1-3) was followed by the plum extract group. Significantly different from the alloxan-only (C2) group the blood glucose levels of alloxan-treated rats could be suppressed by plum extract administration. According to the study data significant differences were found after alloxan treatment for all groups except T1 who received plum extract at 100 mg per kg body weight per day and T2 who received plum

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extract. Mean blood glucose values were similar or slightly different after administration of alloxan at a daily dose of 200 mg/kg body weight. Glycemic data were similar or slightly different between group T3 which received 300 mg/kg B.W./day of plum extract and group (C1) which also did not receive alloxan or plum extract. between T2 given 200 mg/kg B.W./day plum extract and T3 given 300 mg/kg B.W./day plum extract.

Hepar Microscopic Examination

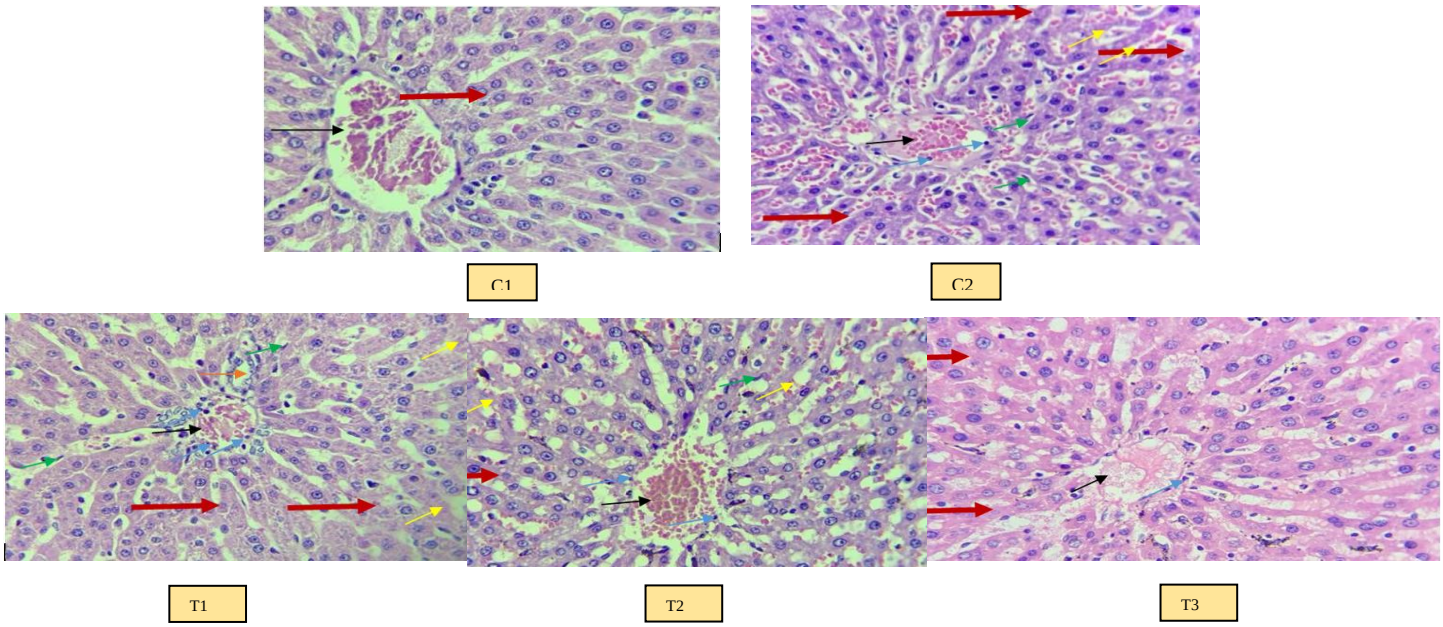

Figure 3. The red arrow shows degeneration of hepar cells, and the yellow arrow shows Necrosis of hepar cells, the blue arrow shows inflammatory cells, the green arrow shows kupffer cells, the black arrow shows hepatic portal vein, the light brown arrow shows billiaris duct, the sinusoid widened. (400x magnification, Hematoxylin, and Eosin colouring).

The results showed that alloxan-induced liver necrosis and the use of plum extract at a dose of 100 mg/kg B.W./day failed to reduce necrosis in the group that did not receive alloxan or plum extract (C1). Significant difference of necrosis score with positive group (C2) and treatment group 1 (T1). On the other hand the number of necrosis scores was not significantly different between groups treated with alloxan or plum extract C1 T2 that did not receive plum extract at a dose of 200 mg/kg B.W./day and group 3 after alloxan treatment. (T3) which received plum extract at a dose of 300 mg/kg B.W./day after receiving alloxan. This shows that there is a significant difference between the plum extract group (C1) at a dose of 200 mg/kg B.W./day that received only alloxan T2 and the group that received plum extract at a dose of 200 mg/kg B.W./day. day T3. Plum extract at a dose of 300 mg/kg B.W./day. This shows that the use of plum extract at 200 mg/kg feed/day and 300 mg/kg feed/day can reduce necrosis. On the other hand the positive group (C2) was given alloxan only with T1 and plum extract at 100 mg/kg B.W. / day There was little difference in the mean necrosis score of plum extract at a dose of 100 mg/kg B.W. / day failed to reduce necrosis. Treatment group 1 (K.P. 1) was given plum extract 100 mg/kg B.W. / day after alloxan administration has a significant difference with T2. They were given plum extract 200 mg/kg B.W. / day after alloxan administration which means that the degree of necrosis assessment is not the same. On the other hand plum extract given T2 200 mg/kg B.W. / day was slightly different from T3 given plum extract 300 mg/kg B.W. / day which means that the degree of necrosis assessment is almost the same or slightly different.

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DISCUSSION

Diabetes mellitus caused by Alloxan significantly increased blood glucose levels in rats[13]. Alloxan and glucose share considerable structural similarities (molecular morphology). It occurs in aqueous solution as alloxan monohydrate a hydrophilic B-cell-killing glucose analog. As a hydrophilic molecule glucose cannot cross the lipid bilayer of the plasma membrane nor can it enter the cytoplasm by itself. Instead it spreads through a complex diffusion mechanism that uses the transporter GLUT2 found in the plasma membrane of cells. Due to the structural similarity between alloxan and glucose GLUT2 facilitates their passage across the plasma membrane of β cells into the cytoplasm[14].

Alloxan is susceptible to redox cycling because it is an unstable molecule. In the presence of intracellular thiols especially glutathione (GSH) alloxan undergoes a continuous and continuous cyclic reaction that produces reactive oxygen species (ROS) such as superoxide radical ions (O2) and hydroxyl radicals (OH). Dialysate reducing products. During the process alloxan is converted to dialysate which is converted back to alloxan[14].

Several secondary metabolites have been shown in vivo and in vitro to exert glucose-lowering activity and to affect multiple protein and enzyme targets in published studies. Alkaloid phenols anthocyanins flavonoids saponins tannins terpenes and coumarins have been shown to have important antidiabetic effects[15]. Phenols are a diverse class of biologically active secondary metabolites composed of the shikimate and acetate pathways. Simple phenols also called phenolic acids are classified into four groups: coumarins lignans lignins stilbenes tannins and flavonoids. Flavonoids include flavanols flavonols flavanones isoflavones and anthocyanins[16].

The flavonoid tannins and triterpenoid saponins found in plums protect the function of pancreatic cells by increasing insulin production which lowers blood glucose levels. Peroxisome proliferator-activated receptors (PPARs) are also activated by flavonoids. The abundant library of useful natural products and nuclear receptor ligands are considered as potential therapeutic targets. Knowing the regulatory mechanisms and transcriptional targets of the peroxisome proliferator-active receptor (PPAR) and other related receptors should provide a comprehensive understanding of the pathogenesis of diabetes as a means for designing rational treatments[17].

Mahajan et al.[17] reported antidiabetic benefits of multiherbal preparations are mainly flavonoids triterpenoids and alkaloids. These compounds either increase insulin levels or decrease glucose uptake in the stomach.

In diabetes mellitus, hyperglycemia directly affects reactive oxygen species (ROS). ROS are linked to oxidative stress, which is crucial for the beginning and development of diabetic neuropathy[18]. Saponins have been proven to exhibit antioxidant properties in both in vitro and in vivo settings[19]. The saponin structure consists of multi-O.H. The group offering this property. This structural feature is responsible for preventing ROS formation in diabetes. Saponins can also increase catalase and superoxide dismutase (SOD) which are generally reduced in diabetic animal models[18]. Activation of antioxidant enzymes reduces ROS formation in diabetes. As blood sugar levels rise serum lipid levels rise which is a risk factor for coronary heart disease. Saponins control hyperlipidemia (by modulating leptin adiponectin and other lipid metabolism-related genes) and reduce insulin resistance by modulating the expression of several lipid metabolism-related genes[18]. Furthermore, saponins increase the expression of PPAR, a transcriptional factor that regulates adipogenesis and decreases blood cholesterol and triglyceride level[17]. Triterpene saponins also inhibit glucose efflux from the stomach into the small intestine by interacting with the glucose-1 transporter. This precipitates intestinal mucosal proteins and forms a protective intestinal barrier that lowers blood sugar levels by reducing glucose absorption across the intestinal membrane. Variable blood sugar levels can affect how the dose of each therapy and extract is calculated[20]. Plum extract effectively reduces blood glucose levels in alloxan-treated rats at T3 at 300 mg/kg B.W./day. The T1 dose of egg yolk extract is 100 mg/kg B.W. /day and T2 doses of 200 mg/kg B.W./day did not significantly reduce blood glucose levels in rats given alloxan.

Necrosis is cell death. Dead cells have small nuclei and abundant chromatin and reticular fibers. The nuclei are thick and dark (repressed) and may be fragmented or fragmented. The cell nucleus is completely dissolved (nucleolysis) and is no longer

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visible. Mechanisms of necrosis occur when tissues are exposed to hypoxia or when toxic foreign substances are introduced. When mitochondria are damaged ATP reduces Na and the K pump fails. When Na enters the cell the lysosomes burst and release hydrolytic enzymes that break down the cell.

The positive control group (C2) and T1 (plum extract at 100mg/kg B.W./day) were significantly different from the negative control group (C1). T2 (plum extract dose 200 mg/kg B.W./day) and T3 (low dose 300 mg/kg B.W./day) showed little difference from the negative control group (C1). When the positive control (C2)) T1 (100 mg/kg B.W./daily administration of plum extract) was used there was a significant difference from the negative control (C1). T2-3 showed significant changes compared to the positive control (C2). The necrosis score of the T2 group (administered 200 mg plum extract/kg bw/day) was almost the same or slightly lower than that of the T3 group (administered 300 mg plum extract). /kg body weight/day). Different amounts of extracts per dose in different treatments may have different effects in reducing the incidence of hepatocyte necrosis.

Preclinical and clinical evidence indicates that Prunus species can improve energy balance including glucose and lipid metabolism reduce inflammatory mediators reduce fat deposition modulate gut microbiota and so on. Metabolic disorders can alter conditions[6]. This fruit extract is considered safe to use as a natural alternative to conventional treatments and has many potential benefits. Further testing of the various molecular pathways involved in insulin signaling glucose/lipid homeostasis oxidative stress inflammatory cascade and blood pressure regulation was performed in D.M.

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