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# Studying the Effects of *Capparis Spinosa* Hydroalcoholic Extract on Glucose Metabolism Pathways in Rat Liver Cells

**Mirko Marino, Patrizia Riso, Sabika Allehdan, Mariangela Rondanelli*, Simone Perna, Ayesha Rafique**

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## Abstract

It is necessary to find new drugs with fewer side impacts to decrease sugar in diabetics. This research aimed to investigate the impact of *Capparis spinosa* extract on the vital enzymes of glucose metabolism in diabetic male rats' liver cells. In the current study, a total of 60 rats were randomly divided into 6 groups. Diabetes was induced by streptozotocin intraperitoneal injection at a dose of 50 mg/kg. Insulin hormone and serum glucose were measured with the relevant kit, the activity of hexokinase and glucokinase enzymes was done by manual method and the expression of glucose 6 phosphatase and phosphofructokinase gene was done by Real Time-PCR method. Data were analyzed using the Kruskal-Wallis non-parametric test and Mann-Whitney post hoc test. The obtained results showed that the administration of the extract reduced the glucose serum level and increased the serum level of glucokinase and insulin and the phosphofructokinase-1 genes expression level in all groups receiving the extract compared to the control groups, and the average activity of the hexokinase enzyme and the expression of the glucose gene 6 phosphatase showed a significant difference among most groups (P<0.001). According to the findings, the treatment of diabetic rats with *Capparis spinosa* extract causes a significant reduction in blood sugar and an increase in the serum insulin amount and also causes an improvement in the enzyme activity involved in glycolysis. Thus, it seems that the consumption of this fruit has a good impact on insulin secretion, blood sugar, and sugar metabolism.

**Keywords:** Glucose metabolism pathways, Plant extract, Liver cells, Rat

**Mirko Marino, Patrizia Riso, Simone Perna**
Department of Food, Environmental and Nutritional Sciences (DeFENS), Division of Human Nutrition, Università degli Studi di Milano, Milano, Italy.

**Sabika Allehdan, Ayesha Rafique**
Department of Biology, College of Science, University of Bahrain, Sakhir Campus P. O. Box 32038, Bahrain.

**Mariangela Rondanelli***
IRCCS Mondino Foundation, 27100 Pavia, Italy.
Unit of Human and Clinical Nutrition, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, 27100 Pavia, Italy.

***E-mail:** mariangela.rondanelli@unipv.it

## Introduction

Diabetes mellitus is a common disease in the world, which is associated with increased blood glucose, and disturbance in carbohydrate and lipid metabolism. It is estimated that the number of patients with diabetes in the world will increase to 366 million in 2030 (Roberts *et al*., 2017). Deficiency or relative reduction of insulin in this disease is associated with acute and chronic metabolic complications (Abdelsalam *et al*., 2019; Teimouri *et al*., 2022). One of the most important consequences of diabetes is the emergence of oxidative stress conditions in patients (Paul *et al*., 2022). Past studies have shown that increased production of free radicals is involved in the pathogenesis and complications of diabetes and high blood pressure (Byrne *et al*., 2021; Bhatti *et al*., 2022; Liu *et al*., 2022). Also, it has been shown in various studies that oxidative stress in diabetes has an effective role in causing disease complications (Kang & Yang, 2020).

Various factors are known in the production and increase of free radicals in diabetic patients, and one of the most important factors is hyperglycemia, which increases the oxidation of glucose through several pathways and leads to the production of more free radicals. The levels of some prooxidants such as homocysteine and ferritin increase in diabetes. There is a definite relationship between homocysteine levels and lipid peroxidation in diabetic patients, and probably homocysteine is effective in causing vascular damage in diabetes through systems related to increasing the production of oxygen free radicals. Also, a direct relationship between poor glucose control and other complications of diabetes such as retinopathy and nephropathy has been shown, and in contrast to accurate blood glucose control, it leads to a delay in the occurrence of microvascular complications (Linn *et al*., 2023). In diabetes, the balance between free radicals and antioxidants is lost, and due to the increase of oxidants in the body, the process of developing complications of diabetes accelerates (Liguori *et al*., 2018; Ahmad & Ahsan, 2020; Babel & Dandekar, 2021).

Today, many chemical drugs are used to treat diabetes. Although chemical drugs have many beneficial effects, pharmacological and pharmacology knowledge believes that there is no chemical drug that is without complications and harm. Therefore, pharmaceutical science is looking for ways to achieve drugs that have minimal side effects (Adwan & Omar, 2021). Currently, the use of herbal and natural medicines instead of chemical medicines is an issue that

has gained importance. Today, it is known that medicinal plants have countless compounds, these compounds create a very balanced situation next to each other and adjust each other's properties, and some compounds have exactly the task of neutralizing the effects of other compounds (Adwan & Omar, 2021).

*Capparis spinosa* belongs to the Capparidaceae family. The *Capparis spinosa* has aromatic compounds that grow wild in hot and dry areas such as West and Central Asia and the Mediterranean region (Ouhammou *et al*., 2022). The used parts of the plant are its buds or flower-producing pieces, which are usually placed in vinegar for about three months after picking, or those that are kept in salt water and then consumed. Its fruit, root, and skin are mostly used for therapeutic purposes; the effective ingredient of this plant is quercetin (Ouhammou *et al*., 2022). The results of examining the chemical composition of *Capparis spinosa* fruit essential oil showed that terpenoids and sulfur compounds are the main components of the essential oil. Thymol (1.24%) included the most terpenoid compound. Different types of isothiocyanates (2.29%) were observed in the essential oil, which mainly included methylsulfonyl heptyl isothiocyanate (5.12%), and isopropyl isothiocyanate (1.6%) (Sanchooli *et al*., 2012).

Considering that finding new drugs with fewer side effects, more effectiveness and less cost to reduce blood sugar and fat in diabetic people seems necessary and considering that so far there has been very limited research on the properties of *Capparis spinosa* (Sanchooli *et al*., 2012; Kumari *et al*., 2019; Adwan & Omar, 2021; Ouhammou *et al*., 2022), as a result of this study, to determine the effect of *Capparis spinosa* hydroalcoholic extract on the key enzymes of glucose metabolism in the liver cells of diabetic rats.

## Materials and Methods

The current study was of an experimental type in 60 male Wistar rats were randomly selected from among male rats with an approximate weight of 250-300 grams, which were in the same climatic conditions with a temperature of 20-22 C° and a relative humidity of 30-70%. and the dark or light cycle of 12 hours was kept, were selected, and randomly divided into 6 groups of 10.

First, the fruits of the *Capparis spinosa* plant were washed and dried in the shade, and then they were powdered using a Moulinex mill (made in France) and 10 grams of powder were added to the volume of 100 ml. The intended solvent in this study was 70% ethanol, which was added to the powder and the mixture was kept in laboratory conditions for 48 hours, to prevent alcohol evaporation, the opening of the Erlenmeyer flask was closed with parafilm. Then the mixture was passed through S&S laboratory filter paper with a diameter of 125 mm made in Germany. First, the extract was placed in a vacuum oven and the solution was turned into a dry powder using a freeze dryer (Zirbus Technology, Germany). To prepare oral solutions for oral administration (gavage) to the studied animals, extract powder with doses of 200 and 800 mg per kilogram of animal body weight was dissolved and prepared in 5 ml of solvent (distilled water). The extract solutions were kept in the refrigerator until use. This procedure was performed just before administration and daily.

To induce diabetes in animals from Streptozotocin; STZ was used in the amount of 50 mg/kg as an intraperitoneal injection. 5 days after the injection, the blood sugar of the rats was measured, and to confirm diabetes, a blood sample was taken from the tail vein, and sugar above 180 mg/dL was considered as diabetic. Rats were divided into three groups. Considering the metabolic changes and differences in the bodies of diabetic and healthy rats, we also examined three groups of healthy rats.

60 mice were randomly divided into 6 groups. Group 1, normal rats that received only distilled water. Group 2, normal rats that received a concentration of 200 mg/kg extract. Group 3, normal rats that received a concentration of 800 mg/kg extract. Group 4, diabetic rats that received only distilled water. Group 5, diabetic rats that received a concentration of 200 mg/kg extract. Group 6, diabetic rats that received a concentration of 800 mg/kg extract. All procedures of working with laboratory animals were done by the instructions of the ethics committee of the university. To measure blood sugar levels, diabetic and healthy rats were anesthetized, and blood was taken from the corner of the eye. After 42 days of administration of *Capparis spinosa* fruit extract by injection, blood was taken from the hearts of rats and the experiments were repeated.

The tested sample was serum, and the blood sugar of rats was measured, sugar above 180 mg/dL was considered as diabetic, and also the serum level of insulin hormone was measured using a special rat insulin measurement kit (Sweden, Mercodia) and the results were between The groups were compared after 6 weeks.

After the completion of the study (sixth week), the liver tissue of the animals was taken out and aliquoted in 4 separate microtubes and immediately transferred to the liquid nitrogen tank. For complementary DNA (cDNA) synthesis, 1 microgram of total ribonucleic acid (RNA) was incubated with 1 microgram of random hexamer for 5 minutes at 70°C. Then this mixture was transferred to the tube containing the cDNA master mix. The mixture was placed in a thermocycler for 60 minutes at 42°C to synthesize cDNA, then it was placed at 95°C for 5 minutes to inactivate the reverse transcription enzyme. At this stage, the necessary amount of synthesized cDNA was removed and mixed with a master containing Taq DNA polymerase and the rest of the required materials, and RT-PCR was performed in 40 cycles. The PCR program included a temperature of 96°C for 10 seconds to denature the cDNA, and a temperature of 70°C for 5 seconds was used for annealing and synthesis. The primers used included the specific forward and reverse primers of each gene whose sequence was designed. Cybergreen was used to monitor each stage, which is a fluorescent reporter molecule that shows the state of proliferation in each stage. The target gene concentration was stated relative to the β-actin housekeeping gene concentration. β-actin was utilized as an internal standard. Data were investigated by BIORAD CFX manager software version 2015.

The activity of glucokinase and hexokinase enzymes was measured manually. Briefly, first, one gram of liver tissue was separated, fragmented, and homogenized with an ultrasonic

homogenizer (NexTgen Lab500, France). After centrifugation (Hettich, Germany, EBA200), the upper clear solution was used. It should be noted that all the above steps were repeated to measure each of the enzymes. Then according to valid protocols for each enzyme (Sakrani *et al*., 2022), by providing the relevant substrate and drawing a standard curve, the level of enzyme activity was determined and compared.

Statistical analysis was done by SPSS software version 23. Results are reported as "(third quartile - first quartile) median". The homogeneity of the variance of the groups was evaluated by Levene's test and the normality of the data distribution was evaluated by the non-parametric Kolmogorov-Smirnov test. Due to the lack of normal distribution (P<0.05), the Kruskal-Wallis non-parametric test and Mann-Whitney post hoc test were used to compare the mean of the groups. The level of significance in the tests was considered 0.05.

## Results and Discussion

The findings of the study showed that *Capparis spinosa* fruit extract significantly decreased the mean serum glucose level in all groups receiving the extract compared to the groups receiving distilled water **(Table 1)** (P<0.001). Also, the findings of the Mann-Whitney test revealed that there was a statistically significant difference in all pairwise comparisons (P<0.001), only the mean of the serum glucose levels of normal rats that received different concentrations of 200 and 800 mg/kg extract. There was no statistically significant difference (P=0.796).

The mean serum level of insulin was increased in all groups receiving the extract compared to the groups receiving distilled water (P<0.001) **(Table 1)**. The findings of paired group comparisons revealed that the median insulin serum level between the groups of normal rats did not have a statistically significant difference (P<0.05) and in the paired comparisons of diabetic rats, the median insulin serum level that different doses of 200 and 800 mg/kg extract had received, there was no statistically significant difference (P=0.853). Other paired group comparisons showed significant differences between the two groups of healthy and diabetic rats (P<0.001).

The mean activity of the glucokinase enzyme was increased in both diabetic and healthy rats receiving the extract compared to the group receiving distilled water (P<0.001) **(Table 1)**. The results of pairwise comparisons of normal mice did not show a statistically significant difference (P<0.05) and in the group of diabetic mice, only the median difference of the groups receiving the extract with different concentrations of 200 and 800 mg/kg was not statistically significant (P = 0.853) and other group pair comparisons and also between two groups of healthy and diabetic mice were statistically significant (P<0.001).

**Table 1.** Comparison of mean serum levels of glucose, insulin, and glucokinase enzyme activity levels in different concentrations of *Capparis spinosa* extract.

| Groups | Glucose (mg/dL) Median (Q1-Q3) | Insulin (µg/L) Median (Q1-Q3) | Glucokinase (mu/mg protein) Median (Q1-Q3) |
|---|---|---|---|
| Group 1 | 122.24 (121.67-122.57)[a] | 1.81 (1.77-1.84)[a] | 6.26 (5.88-6.62)[a] |
| Group 2 | 107.92 (107.55-108.81)[b] | 1.82 (1.73-1.92)[a] | 6.55 (6.47-6.62)[a] |
| Group 3 | 108.25 (105.54-109.94)[b] | 1.83 (1.77-1.90)[a] | 6.91 (6.40-7.54)[a] |
| Group 4 | 245.65 (240.32-247.60)[a] | 0.30 (0.28-0.32)[b] | 3.10 (3.09-3.12)[b] |
| Group 5 | 213.58 (212.34-214.94)[a] | 0.40 (0.35-0.56)[c] | 4.17 (4.11-4.23)[c] |
| Group 6 | 195.89 (192.43-197.45)[a] | 0.41 (0.37-0.48)[c] | 4.06 (3.91-4.28)[c] |
| P-value* | < 0.001 | < 0.001 | < 0.001 |

* Kruskal-Wallis non-parametric test

According to the Mann-Whitney post hoc test, in each variable, groups with different English letters have a statistically significant difference in the mean (P<0.001).

The findings of the study also revealed that *Capparis spinosa* fruit extract significantly increased the median expression of the phosphofructokinase-1 gene in all groups receiving the extract compared to the groups receiving distilled water (P<0.001) **(Table 2)**. The findings of paired group comparisons revealed that in the group of healthy and diabetic rats, there is no significant difference between the mean expression of the phosphofructokinase-1 gene in the two groups receiving extracts with different concentrations of 200 and 800 mg/kg (P<0.05) and other comparisons Group pair is significant (P<0.001).

The mean expression of the glucose-6-phosphatase gene in the studied groups had a statistically significant difference **(Table 2)** (P<0.001). Also, the results of group pairwise comparisons showed that the average expression of this gene between healthy mice did not differ significantly (P<0.05). Pairwise group comparisons in the group of diabetic rats also showed that the only difference in the mean of this gene in the group receiving distilled water and the group receiving the extract with a concentration of 200 mg/kg was not significant (P=0.998). Other pairwise group comparisons were statistically significant (P<0.001).

The mean activity of the hexokinase enzyme in the studied groups had a significant difference (P<0.001) **(Table 2)**. The results of paired group comparisons showed that in healthy mice, only the mean of hexokinase enzyme activity between the group receiving distilled water and the group receiving the extract with a concentration of 800 mg/kg was not significant (P=0.739). Group pair comparisons showed that in diabetic rats, only the mean of hexokinase enzyme activity between the group receiving distilled water and the group receiving extract with concentrations of 200 and 800 mg/kg was not significant (P<0.05). Other pairwise

comparisons between the two groups of diabetic and healthy rats were statistically significant (P<0.001).

**Table 2.** Comparison of the average expression level of phosphofructokinase-1, glucose-6-phosphatase genes, and hexokinase enzyme activity due to different concentrations of *Capparis spinosa* extract.

| Groups | Phosphofructokinase gene (Folding) Median (Q1-Q3) | Glucose-6-phosphatase gene (Folding) Median (Q1-Q3) | Hexokinase enzyme (mu/mg protein) Median (Q1-Q3) |
|---|---|---|---|
| Group 1 | 1.00 (0.99-1.00)[a] | 0.99 (0.98-1.01)[a] | 8.12 (7.82-8.40)[a] |
| Group 2 | 1.26 (1.21-1.30)[b] | 1.03 (0.98-1.08)[a] | 7.78 (7.69-7.96)[b] |
| Group 3 | 1.28 (1.26-1.30)[b] | 0.99 (0.94-1.02)[a] | 8.13 (8.09-8.24)[a] |
| Group 4 | 0.64 (0.63-0.66)[c] | 1.19 (1.18-1.20)[b] | 5.71 (5.62-5.93)[c] |
| Group 5 | 0.70 (0.67-0.75)[d] | 1.21 (1.17-1.23)[b] | 6.19 (6.08-6.24)[c] |
| Group 6 | 0.74 (0.71-0.77)[d] | 1.33 (1.32-1.34)[c] | 5.86 (5.65-6.44)[c] |
| P-value | < 0.001 | < 0.001 | < 0.001 |

* Kruskal-Wallis non-parametric test

According to the Mann-Whitney post hoc test, in each variable, groups with different English letters have a statistically significant difference in the mean (P<0.001).

*Capparis spinosa* is one of the aromatic plants that has various properties, including reducing the serum level of blood sugar and fat (Yang *et al*., 2022). According to the results of this study, the administration of *Capparis spinosa* extract was able to significantly decrease the glucose levels of hyperglycemic (experimental) mice caused by streptozotocin injection. It also increased the level of serum insulin, glucokinase enzyme activity, and phosphofructokinase-1 gene expression in all groups receiving *Capparis spinosa* fruit extract compared to control groups. The average activity of glucose-6-phosphatase gene and hexokinase enzyme had a significant difference in different groups. The results of previous research indicate that some medicinal plants, such as *Capparis spinosa*, slow down the digestion and absorption of carbohydrates in the digestive system, cause the gradual entry of glucose into the blood, and prevent the sudden increase in blood sugar after eating (Assadi *et al*., 2021).

Based on the results of Assadi *et al*.'s research on *Capparis spinosa*, it was found that feeding the aqueous extract of its fruit to rats with a high-fat diet reduced the serum level of blood sugar and fat in these rats. In fact, due to the presence of various fibers and antioxidants such as phenols, these plants reduce the serum level of sugar and fats. Because *Capparis spinosa* is rich in such compounds, it activates anti-fat and anti-hyperglycemic pathways in the body, which confirms the findings of our study (Assadi *et al*., 2021). In addition, *Capparis spinosa* is rich in quercetin, which is known to lower blood glucose (Paul *et al*., 2022). In a study, it was shown that dyslipidemia in diabetes is a main risk factor for cardiovascular diseases (Kumari *et al*., 2019). Their results showed that the disorder in the lipid profile of diabetic rats was not only corrected by the consumption of *Capparis spinosa* extract but also caused a significant increase in cholesterol, plasma TG, and LDL-C levels and a significant reduction in HDL-C levels in diabetic rats. The cholesterol-lowering activity of fruit extract may be due to the reduction of intestinal cholesterol absorption, and the reduction of cholesterol leads to the increase of LDL receptors and LDL absorption (Kumari *et al*., 2019). In another study, the protective impact of the extract on the levels of liver enzymes was reported (Kazemian *et al*., 2015; Vickers, 2017). In other studies, the therapeutic effect of Cor extract has been attributed to the quercetin presence in this extract (Mollica *et al*., 2017).

Oxidative stress and hyperglycemia play an important role in the development of diabetes complications. Continuous hyperglycemia increases the production of ROS (Reactive oxygen species (Kuate *et al*., 2015; Soliman, 2016). Some studies have shown the antioxidant properties of *Capparis spinosa* in diabetic rats and also showed that *Capparis spinosa* contains antioxidant compounds that may prevent ROS-induced liver damage due to increased levels of reduced glutathione (GSH) as a scavenger, reduce the main free radicals (Okur *et al*., 2018). In line with the present results, previous studies showed that *Capparis spinosa* extract had the effect of reducing blood lipids in diabetic rats (Van Veen *et al*., 2010), so this extract may be considered a food supplement for diabetic patients (Archana *et al*., 2022; Sun *et al*., 2023).

It has been reported that the extract of this plant is used in traditional medicine to cure various ailments such as rheumatism, rheumatoid arthritis, and gout (Aliyazıcıoglu *et al*., 2013; Moutia *et al*., 2016). In Zhang *et al*. study, the improvement of hypertriglyceridemia and hyperglycemia in diabetic patients was shown by *Capparis spinosa*. In addition, no renal and hepatic side effects were reported in the patients. On the other hand, the results of their study indicate the lack of hepatotoxicity of Kor plant extract in human doses (Zhang & Ma, 2018). This plant has high amounts of phenolic compounds. It also seems to be an important source of tocopherol including α-tocopherol and γ-tocopherol. In addition, high amounts of carotene have been observed in this plant (Wojdyło *et al*., 2019). *Capparis spinosa* in appropriate doses does not have toxic effects on human body tissues and can probably be used as a supplement in reducing blood sugar. Of course, more research should be done in this field.

## Conclusion

Considering the beneficial effects of the administration of *Capparis spinosa* extract in reducing sugar and increasing the amount of blood insulin in healthy and diabetic rats, as well as

improving the activity of liver enzymes involved in sugar metabolism, it seems that after conducting clinical trials, *Capparis spinosa* can be used in discount Complications of hyperglycemia and diabetes used.

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