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RESEARCH PAPER

Topical Application of Capparis Spinosa Fruit Extract Lowers Blood Glucose Level

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A B S T R A C T:
Wounds are a nightmare for people with diabetes due to the fact that they tend to heal slowly or do not heal well. Blood glucose levels, a major contributor to wound complications, must be lowered to facilitate wound healing. A medicinal plant extract with known hypoglycemic properties can be of great opportunity in curing diabetic wounds. *Capparis spinosa* fruit has long been used as an anti-hyperglycemic food in traditional Middle Eastern herbalism. For the first time, the capacity of caper berries to lower blood glucose levels by direct local application to the wound was proved in this study. The study was conducted using 20 male Wistar rats. Each rat was given a single dose of Alloxan (150 mg/kg) intraperitoneally. Surgical incisional wounds with full-thickness skin and a length of 1.5 cm were made in the skin of each rat, then the rats were randomly divided into Group A: 10 rats with a daily local application of the extract on the wound. Group B: 10 rats with normal saline applied topically. Blood glucose levels were evaluated daily until the end of the trial. According to an independent t-test, there was a highly significant difference (p 0.01) in the mean values of blood glucose levels between groups A and B at three days and a significant difference (p 0.05) in blood glucose levels recorded at seven days' duration. The results provide support for the use of *Capparis spinosa* fruit extract in managing hyperglycemia and preventing the complications associated with it in diabetics.

KEY WORDS: Capparis Spinosa, Capparaceae, diabetic, Hypoglycemic
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1.INTRODUCTION:

Capparis spinosa, commonly known as caper, is a plant species that has been traditionally used in Middle Eastern cuisine as a condiment and for its medicinal properties. In recent years, there has been increasing interest in the potential of *Capparis spinosa* to treat diabetes (Eddouks et al., 2017). Plant essential oils and plant extracts can also be used as wound dressings. When a person applies the plant extract directly to the skin, some of the particles may be tiny enough to penetrate the skin, where they may enter the bloodstream or give localized therapy. Many of these extract components are easily absorbed by the body (Sarkic and Stappen, 2018). Diabetes develops when the body is unable to produce or utilize insulin adequately.

Insulin is a hormone that helps regulate blood glucose levels, and if not enough of it is present, health complications might result (Arthur and Chausmer, 1998). There are many types of diabetes that can result from genetic factors or lifestyle choices. Conventionally, several studies have found that diabetes mellitus can mediate a variety of consequences, including diabetic cardiovascular problems, diabetic neuropathy, retinopathy, nephropathy, and liver issues, which are the leading causes of death and morbidity in the disease (Mukhtar et al., 2020) (Pourhanifeh et al., 2020). As a logical consequence, it is essential to look for effective ways to lower blood glucose levels so that diabetes mellitus complications can be prevented, or if not prevent, then at least managed.

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The caper (*Capparis spinosa L.*), a member of the genus Capparis (Capparidaceae family), is found all over the world. Different portions of C. spinosa have been used in traditional medicine to treat a variety of chronic human diseases such as diabetes, asthma, convulsions, and rheumatism. The caper is high in glucosinolates, tannins, coumarins, saponins, and flavonoids such as quercetin, rutin, kaempferol, and quercetin derivatives (Mirzakhani et al., 2020). Whatever the forms in which they are metabolized, these chemicals are exceedingly complicated in structure and chemical composition, and they have been found to have potential applications for human health in addition to having a recognized therapeutic activity that is featured in many pharmacological activities (Bouskout et al., 2022). The chemical components of bioactive chemicals in *Capparis spinosa* fruits, leaves, and roots have been researched, as well as their value for human health.

Diabetic wounds are distinct from non-diabetic wounds. High blood glucose is an ideal environment for the growth of bacteria, and if this growth of bacteria occurs in diabetic ulcer patients, it will result in infection. This wound should be treated immediately to avoid further damage and possible amputation. However, there have been in vitro and animal studies that suggest that Capparis fruit extract may have potential wound-healing properties (Amiri et al., 2015) (Kalantar et al., 2018). Furthermore, research including using Capparis fruit extracts to facilitate wound healing in diabetes has been proven in vivo study (Alwan and Ghani, 2020). Therefore, the present study aims to determine the effect of *Capparis spinosa* ethanol extract on the blood glucose level in experimental diabetes rats.

The phytochemical composition of *Capparis spinosa* fruits was characterized by using Gas Chromatography-Mass spectrometry (GC-MS). Thirty-five active chemical compounds were recognized in the *Capparis spinosa* extracts; functional chemical compounds were identified based on their molecular weight, retention time, molecular formula, and peak area. GC-MS analysis revealed the presence of a highly complex molecule.

2. MATERIALS AND METHODS

2.1. MATERIALS

2.1.1 Plant Material Collection:

Capparis spinosa fresh fruits were collected by hand from several rural areas around Baghdad. The fruits were identified and authenticated by the Department of Pharmacognosy and medicinal plants at ALMustansiriyah University, College of Pharmacy. Fruits were thoroughly washed, cut into small pieces, and dried in the shade at 25°C.

2.1.2 Preparation of Fruit Extracts

In the preparation of the *Capparis Spinosa* alcoholic extract, the dried fruits of capers were ground into powder using a home coffee grinder. Then, at the pharmacology lab, using a Soxhlet extractor, 200 gm of caper fruit powder was poured into a one-liter flask, and 70% ethyl alcohol was added to the powder. The solution was filtered after 72 hours, and the ethanolic extract was concentrated under reduced pressure evaporation using a 50°C rotary evaporator with a rotating speed of 70 rpm to one-third of the initial quantity.

2.2. Phytochemical Screening by GC-MS Analysis:

Gas chromatography is a technique for separating the components of a crude and producing a spectral signature for each one. The technique involves introducing the sample into the injection port of the gas chromatography equipment, which vaporizes it. Following vaporization, the various components can be separated and analyzed as each of them results in a different spectral peak. The ethanolic extract of C. spinosa was GC-MS analyzed using the Willey and NIST libraries, with retention indices compared.

2.3.Animal preparation:

All experiment operations were carried out in compliance with Baghdad University's College of Dentistry's experimental animal ethical guidelines No 008718. To determine the sample size, we used a G-power sample size calculator. The study was conducted using twenty healthy male Wistar rats weighing between 250 and 300 g. The laboratory rats were randomly divided into two groups: A control (ten rats) and B experimental (ten rats). They were separated into different cages and a red marker was used to give sequence numbers to each rat, so as to be able to differentiate between individual animals used in the study. For each animal, two investigators work together: one to weigh the animals and calculate the accurate dose of alloxan; the second one is responsible for the injection, daily monitoring of blood glucose level, and surgical incision; both are responsible for daily local application of Capparis spinosa extract. All of this is done under the supervision of a veterinary doctor.

The animals in both groups were weighed to calculate the accurate dose of alloxan administered to them. Diabetes was induced in rats by injecting 150 mg/kg B.W of Alloxan intraperitoneally (Macdonald Ighodaro et al., 2017).

Every day, blood glucose was recorded until the experiment is completed. After 12 hours of fasting, blood was gathered from the animal’s tail. The tail was embedded in alcohol, about one millimeter of its end was clipped, and a few drops of blood were used for the blood sugar assessment with the aid of a glucometer. The animals with a blood glucose level greater than 11.1 mmol/L were stated to be hyperglycemic and included in the study. After five days, if the animals' blood glucose levels did not reach 11.1 mmol\L, they were excluded and replaced.

The total number of laboratory animals used in this study was twenty-five. At the beginning of the experiment, Group B contained ten adult male rats. A few days later, the number increased to n = 15 due to the exclusion of three male rats that did not develop hyperglycemia and the death of two rats due to diabetic complications in the early days of the experiment.

Following the induction of general anesthesia, surgical incisional wounds with full-thickness skin involve both the epidermis (the outermost layer of the skin) and the dermis (the layer beneath the epidermis), and a length of 1.5 cm were made in the skin of each rat. All of the animals in group A received daily local applications of a Capparis spinosa extract dose of 200 mg/kg, and the animals in group B had normal saline applied topically.

2.4. Statistical Analysis

For data analysis, IBM SPSS Statistics software V26 was used. The independent-samples t-test was conducted to determine whether there was a difference between the two independent groups.

3. RESULTS AND DISCUSSION

3.1. Estimation of blood glucose levels:

Every day, blood glucose levels were recorded. The effects of local application of Capparis spinosa extracts on the blood glucose in the diabetic treated rats in group A and the diabetic rats where normal saline was applied in group B, the highest mean value was reported in group B at seven days' duration and the lowest mean value was reported in group A at three days. These findings are also demonstrated in Figure 1.

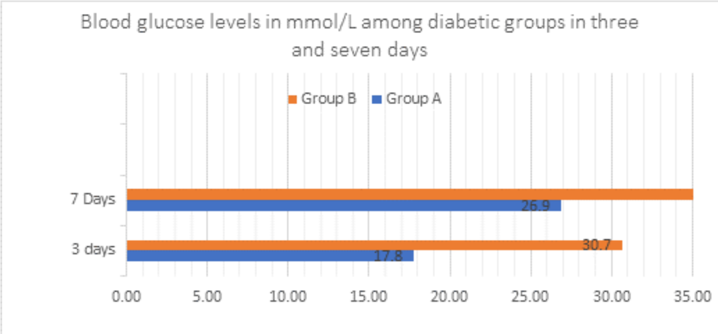

Figure 1: Blood glucose levels among diabetic groups in each healing period

According to the independent t-test, Table1, there was a highly significant difference (p<0.01) in the mean values of “blood glucose levels” at three-day healing interval between groups A and B, and a significant difference (p<0.05) in blood glucose levels at seven-day duration.

Table 1. Independent t-test of blood glucose levels compares between diabetic groups in each healing period

Day	Mean ± SD of Blood glucose		T-test	P-value
	Group A	Group B		
3 days	17.8 ± 7.7	30.7 ± 3.2	3.459	** 0.0086
7 days	26.9 ± 5.7	33.1 ± 0.5	2.423	* 0.0417

* (P<0.05) significant, ** (P<0.01) High significant

3.2. Chromatographic Analyses:

Identification of phytocompounds was based on the values of retention time, molecular weight (MW), molecular formula, and concentration (peak area %). Thirty-five volatile chemicals in Capparis fruit were detected and measured. Figure 2 illustrate the presence of bioactive phytochemical compounds in the ethanolic extract of *Capparis spinosa* in terms of the area percentage concentration (peak area percent) with their retention time (RT), molecular formula, and molecular weight (MW).

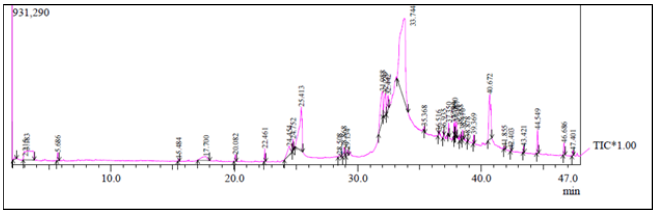

Figure 2. GC-MS Chromatogram of ethanolic extract of *Capparis spinosa* fruit

The result revealed the presence of 35 compounds Table 2 The major constituents were found to be: (cis-13,16-Docosadienoic acid 40.61%), (Pentadecanoic acid 12.37%), (9-Octadecenoic acid, 1,2,3-propanetriyl ester, (E, E, E) 8.51%), (Ethyl 9,12-hexadecadienoate 7.55%), (Ethyl 9-hexadecenoate 3.68%), (cis-9-Hexadecenoic acid 2.84%), (Ethyl. alpha. -d-glucopyranoside 2.19%), (9-Octadecenoic acid, ethyl ester 1.84%), (delta. -Tocopherol 1.77%) and other chemical constituents with less than 1% peak area. The presence of various bioactive compounds justifies the use of the fruit of C.

spinosa for various illnesses by traditional practitioners.

Table 2. Cappris spinosa fruit ethanol extract GC-MS analysis

No.	RT	Name of the compound	Molecular formula	Molecular weight	Peak Area %
1	2.215	N-Methoxymethyl-N-methylacetamide	C5H11NO2	117	0.30
2	3.183	Glycerin	C3H8O3	92	7.29
3	5.686	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl	C6H8O4	144	0.63
4	15.484	Dodecanoic acid	C12H24O2	200	0.16
5	17.700	Ethyl. alpha. -d-glucopyranoside	C8H16O6	208	2.19
6	20.082	Tridecanoic acid	C13H26O2	214	0.55
7	22.461	Hexadecen-1-ol, trans-9-	C16H32O	240	0.66
8	24.454	cis-9-Hexadecenoic acid	C16H30O2	254	2.84
9	24.752	9-Octadecenoic acid, ethyl ester, (E)-	C20H38O2	310	0.64
10	25.413	Pentadecanoic acid	C15H30O2	242	12.37
11	28.508	5-Eicosene, (E)	C20H40	380	0.35
12	28.868	11,14-Eicosadienoic acid, methyl ester	C21H38O2	322	0.93
13	29.134	10-Octadecenoic acid, methyl ester	C19H36O2	296	0.69
14	31.988	Ethyl 9,12-hexadecadienoate	C18H32O2	280	7.55
15	32.229	Ethyl 9-hexadecenoate	C18H34O2	282	3.68
16	32.442	9-Octadecenoic acid, ethyl ester	C20H38O2	310	1.84
17	33.744	cis-13,16-Docosadienoic acid	C22H40O2	336	40.61
18	35.368	Methyl-n-nonyl acetaldehyde	C12H24O	184	0.15
19	36.516	1, E-8, Z-10-Hexadecatriene	C16H28	220	0.15
20	36.935	Docosanoic acid, ethyl ester	C24H48O2	368	0.24
21	37.350	Oleoyl chloride	C18H33ClO	300	0.58
22	37.789	3-Cyclopentylpropionic acid,	C12H23NO2	213	0.48
23	37.850	Octanoic acid	C12H25NO2	215	0.49
24	37.977	10-Undecen-1-al, 2-methyl-	C12H22O	182	0.99
25	38.288	1-Chloroeicosane	C20H41Cl	316	0.41
26	38.470	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	C19H38O4	330	0.53
27	38.878	1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester	C16H22O4	278	0.12
28	39.369	Docosanoic acid, ethyl ester	C24H48O2	368	0.34
29	40.672	9-Octadecenoic acid, 1,2,3-propanetriyl ester, (E, E, E)-		884	8.51
30	41.855	7-Methyl-Z-tetradecen-1-ol acetate	C17H32O2	268	0.18
31	42.403	All-trans-Squalene	C30H50	410	0.11
32	43.421	Tetratetracontane	C44H90	618	0.33
33	44.549	delta. -Tocopherol	C27H46O2	402	1.77
34	46.686	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-	C28H48O2	416	0.98
35	47.401	Heptadecane, 2,6,10,15-tetramethyl-	C21H44	296	0.36
					100.00

Many contemporary medications are derived from medicinal plants. These medications have made substantial contributions to the battle against various diseases and illnesses. Plant material extraction and scientific analysis are essential to the implementation, modernization, and quality control of herbal medicines. As a result, the main objective of this study was to determine the bioactive chemicals present in the ethanolic extract of *Capparis spinosa* using gas chromatography and mass spectroscopy, as well as the influence of Capparis' fruit extract on blood glucose levels. Among the major compounds with more than 40% concentration (peak area %) is docosadienoic acid, which is a Polyunsaturated Fatty Acid PUFA. There are three types of fat in our diet: saturated fat, monounsaturated fat, and polyunsaturated fat PUFAs. Saturated and monounsaturated fats are called nonessential fats, as our bodies can make them. Polyunsaturated fats are essential fats that we need to obtain from our diets(Karakas et al., 2021). Docosadienoic acid is an Omega-6 fatty acid and is a type of polyunsaturated fat found in vegetable oils, nuts, and seeds. PUFAs, like monounsaturated FAs, reduce oxidative stress, inflammation, and endothelial dysfunction, impact insulin secretion and insulin resistance, and lower the risk of diabetes. Several human and animal studies have found that n-3 PUFA can prevent and reverse insulin resistance while also increasing insulin sensitivity (Baynes et al., 2018).

Increased intracellular insulin levels, increased antioxidant enzymatic defense capacity, and decreased pro-oxidant generating activities were the results of PUFAs. In most animal and human experiments, they are correlated with the maintenance of pancreatic beta cell redox status in response to n-3 PUFA. Continuous PUFA supplementation can enhance insulin production and provide considerable resistance to cytokine-induced cell death (Baynes et al., 2018). According to a recent study conducted to determine the effects of polyunsaturated fatty acid sources on lipid, hormonal, blood glucose, weight gain, and histopathological damage profiles in a rat model, PUFAs have a positive impact on improving productive and reproductive hormones, blood glucose, lipid profile, body weight, nutrient digestibility, and ovarian morphology (Komal et al., 2020).

Another meta-analysis study revealed that a low ratio of polyunsaturated fatty acid supplementation could enhance glucose metabolism by lowering insulin and insulin resistance in diabetes patients (Li et al., 2019)

The second and third major compounds in the GC MAS report represent about 20.88% concentration (peak area %) pentadecanoic acid and octadecenoic acid. According to the findings of a recent study, pentadecanoic acid PA, an odd-chain saturated fatty acid SFA, strongly promotes glucose absorption via the AMPK-AS160 pathway and has an insulin-sensitizing impact in myotubes, indicating that it has a direct role in glucose metabolism (Fu et al., 2021). Octadecenoic acid promotes the secretion of GLP-1 (glucagon-like peptide-1), a hormone released from L cells in the small intestine that increases insulin secretion from the pancreas. GLP-1 only secretes insulin when blood glucose levels are high. It is hypothesized that increasing GLP-1 secretion in people with high blood glucose levels is a useful technique for diabetes prevention. pentadecanoic acid activity was greater than that of linoleic acid, a precursor of Octadecenoic acid, implying that lactic acid bacteria's fatty acid metabolism may benefit human health. Octadecenoic acid is a substance with potential for lowering blood glucose levels, and it is predicted to be used in functional foods (Yonejima et al., 2019).

Ethyl 9,12-hexadecadienoate has a concentration of 7.55 percent (peak area %). It is a conjugated dienoic fatty acid metabolite of linoleic acid, a naturally occurring form of linoleic acid positional and geometric isomers that may have significant positive effects on atherosclerosis, carcinogenesis, and obesity in humans (Ciriminna et al., 2017). A recent in vivo study revealed that conjugated linoleic acid significantly lowered fasting blood glucose, increased glucose tolerance, decreased lipid droplet accumulation in the liver, and improved lipid metabolism in mice (Xia et al., 2019).

The two other constituents (Ethyl 9-hexadecenoate and cis-9-hexadecenoic acid) together represent about 6.52 % concentration (peak area %). They are an omega-7 polyunsaturated fatty acid. Their common names are palmitelaidic acid and palmitoleic acid, respectively. Palmitelaidic acid is a trans fatty acid (the trans isomer of palmitoleic acid). A recent study suggests that palmitoleic acid may help improve glucose homeostasis. The findings give a broad rationale for administering omega-3 PUFA-containing phospholipids as nutritional supplements with powerful insulin-sensitizing effects (Rossmeisl et al., 2020).Ethyl alpha-d-glucopyranoside, also known as quercetin, has a concentration of about 2.19% (peak area %) and belongs to the class of chemical compounds known as o-glycosyl compounds. Quercetin improves glucose and lipid metabolism disorders and is probably related to the upregulation and protein level of Sirtuin type 1, as well as its influence on the Akt signaling pathway. As a result, quercetin has the potential to treat glucose and lipid metabolism disorders in diabetes. In the insulin signaling system, protein kinase B (Akt) is essential; activation of the insulin receptor initiates a phosphorylation cascade, which is started by receptor autophosphorylation and the activation of insulin receptor substrate protein (Nitulescu et al., 2018).

The last peak is delta-tocopherol with a 1.77% concentration (peak area %). Delta-Tocopherol is the orally bioavailable form of naturally occurring fat-soluble vitamin E, which is commonly found in soybean and corn oils and has antioxidant activity. Vitamin E has anti-oxidant, anti-inflammatory, anti-obesity, anti-hyperglycemic, anti-hypertensive, and anti-hypercholesterolemic properties (Izadi et al., 2019). Many literature reviews suggest that taking naturally occurring vitamin E as a dietary supplement contributes to the prevention or treatment of metabolic syndrome. More importantly, probable supplementary prophylaxis or therapy with vitamin E will be safe, effective, and highly cost effective in comparison to currently available pharmaceutical medications (Wong et al., 2017).

The current experimental study was conducted to determine the nature of the components responsible for *Capparis spinosa* hypoglycemic action, and it shows clearly that GC-MS is a potent tool for the rapid isolation and characterization of bioactive metabolites. This technique's considerable sensitivity aids in the identification of active compounds in *Capparis spinosa* responsible for its blood-glucose-lowering activity.

4. CONCLUSIONS

This study was conducted to explore the potential blood-glucose-lowering activity of Capparis spinosa fruit extracts in alloxan-induced diabetic rats by direct local application and to explain the obtained results in relation to the active constituents that are responsible for the antidiabetic property. The results showed an improved blood glucose level in less than a week. It is concluded that the ethanol extract of Capparis spinosa induces significant blood glucose lowering in less than a week and appears to be an attractive material for further studies and possible drug development. Further research at the cellular and molecular levels may contribute to understanding its mechanism in a more specific way.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations:

GC-MS: Gas Chromatography-Mass spectrometry
NIST libraries: National Institute of Standards & Technology
M.W: molecular weight
RT: Retention time
PUFA: Polyunsaturated Fatty Acid
SFA: saturated fatty acid
AMPK-AS160: pathway activated protein kinase
GLP-1: glucagon-like peptide-1

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