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ANTI-DIABETIC AND PHYTOCHEMICAL SCREENING OF PROSOPIS JULIFLORA FLOWERS IN STREPTOZOTOCIN MODEL

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Objective:

Prosopis Juliflora is a plant that reported to have anticonvulsant, antimicrobial, antiulcer, and wound healing activities. Diabetes effect of prosopis juliflora leaves is not clear. Hence current study planned to evaluate the antidiabetic effects of methanolic extracts of leaves of Prosopis juliflora in streptozotocin induced diabetic rats.

Materials and Methods: Phytochemicals were determined by standard method. Diabetes was induced by injecting a single dose of STZ (55mg/kg) into female Sprague Dawley rats. After 3 days of induction of diabetes the diabetic animals were treated for 28 days with MEPJ (400mg/kg) and glibenclamide (20mg/kg) orally. The body weight of rats and blood glucose levels were monitored at regular intervals during the experiment. At the end of the study blood sample was collected from all the animals and subjected to biochemical parameters and they were sacrificed and their organs such as pancreas liver and kidney were used for histopathological analysis.

Results: Blood glucose levels presented near 100 mg/dL in control groups. In the diabetic groups, glucose levels were higher than 300 mg/dL. The treatment with MEPJ extract did not interfere significantly with the glycaemia of control or diabetic groups compared with their corresponding groups. The animals of control and treated groups showed no difference in body weight, water and food intake during the study. The body weight in diabetic groups was statistically lower compared to control on days 14 and 20. In addition, the plant treatment caused a reduction in the body weight compared to the diabetic group (non-treated) on days 14 and 20. The rats from diabetic groups presented higher food intake (around 30 g/day) in relation to control groups (about 16 g/day) in all experimental period. In addition, the average water intake was increased in diabetic groups as compared to non-diabetic groups.

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Conclusion: The treatment with aqueous extract of MEPJ leaves given to diabetic rats presented no hypoglycemic effect in non-diabetic animals and no antidiabetic effect in diabetic animals with the doses studied.

Keywords:Prosofis juliflora, Anti-diabetic, Streptozotocin (STZ), MEPJ extract

1 INTRODUCTION

Nature serves humans with medicines which were used to maintain health, to treat and heal many ailments. For the treatment of human diseases a basic product from Natural products like plant, animal and minerals were used. Medicinal plants are of great importance to the health of individuals and communities. Medicinal plants has a potential source of therapeutic aid has attended a significant role in health system all over the world for both human and animals not only in the diseased condition but also has potential material for maintaining proper health. Man ever since his first appearance on earth, has used plant throughout his historical development as a source of medicines. Herbal medicine is a triumph of popular therapeutic diversity. The world is now moving towards the herbal medicine or system, which can then properly fight foreign invaders, and help to destroy offending pathogens without toxic side effects. The world health organization in the early 1970's had encouraged government to effectively utilize local knowledge of herbal medicines for disease prevention and health promotion. WHO has showed great interest in documenting the use of medicinal plants used by tribal's from different parts of the world. The plant kingdom still holds many species of plants containing substances of medicinal values, which have yet to be discovered. We are all aware that India is one of the richest sources of medicinal plants. Interest in medicinal plants has increased enormously over the last two decades

Prosopis juliflora is one of the most economically and ecologically important tree species in arid and semi-arid zones of the world Prosopis juliflora belongs to the family Leguminosae (Fabaceae), sub-family Mimosoideae, and it having 44 species of which 40 are native to the Americas, three to Asia and one to Africa. The tropical Andean region is home to six species and eight species are found in the texas area, seven of them being endemic. These species are having the several properties such as soil binders, sand stabilizers, as well as its ability to grow in the poorest soils. It is a shrub or tree having 8-12 metres long. Growing to a height of up to 12 metres (39 ft), P. juliflora has a trunk diameter of up to 1.2 metres (3.9 ft). Its leaves are deciduous, geminate-pinnate, light green, with 12 to 20 leaflets. Flowers appear shortly after leaf development.

The various chemical agents that are present in it show the medicinal value that may alters certain physiological actions in the human body. The several biochemicals present in the plant are terpenes, alkaloids, flavonoids and phenolic compounds. Terpenes are used as insecticides and their pharmacological properties include antibacterial, antifungal, anthelmintic, antimalarial and molluscicidal. Extracts of P. juliflora seeds and leaves have several in vitro pharmacological effects such as anti-bacterial, anti-fungal and anti-inflammatory properties.Since it is a main source of fuel this plant provides more than 90% of the fuel wood in some Indian villages because P. juliflora wood has excellent burning qualities. Thus, it is called wooden anthracite. It also has high calorific value.

It has been used as a folk remedy for catarrh, cold, diarrhea, dysentery, excrescences, flu, hoarseness, inflammation, measles, sore throat and in healing of wounds. Decoction prepared from leaf and seed extracts are used in wound healing, as disinfectant and also to treat scury. *P. juliflora* syrup prepared from ground pods is given to children showing weight deficiency or retardation in motor development, the syrup is believed to increase lactation. Tea made from *P. juliflora* is

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thought to be good for digestive disturbances and skin lesions. It has soothing, astringent, antiseptic, antibacterial and antifungal properties. It has been used to treat eye problems, open wounds, dermatological ailments and digestive problems by the native tribes of many countries. The flavonoid, patulitrin isolated from its flowers and fruits showed significant activity against lung carcinoma in vivo.. Leaves and pods are to be the richest source of plant metabolite, followed by flower, root and stem. Very high flavonoids content (16%) of Propsopis *juliflora* makes it a potential candidate bearing antioxidant and anticancer properties. Tannins and Phenols although found in low concentrations, (0.33 and0.66% respectively) can synergize the antioxidant and anticancer potential of flavonoids. Phenols are reported to prevent the platelets from clumping and have the ability to block specific enzymes that cause inflammation.

P. juliflora pods are characterized by elevated sugar content, about 300 g/kg of dry matter. With 120 g/kg of crude protein on a DM basis. Once concentrated, the methanolic extract obtained from these beans becomes dark and dense and can be used in beverages and jellies. Roasted and ground, the beans can be used to make a coffee-like beverage.

2 MATERIALS AND METHODS

2.1 Medicinal plant

Leaves of *Prosopis juliflora* were collected and left the sample to dry on trays at ambient temperature in a room with adequate ventilation. Dry conditions were maintained to prevent microbial fermentation and subsequent degradation of metabolites. The dried material was stored in sealed containers in a dry and cool place. After drying, plant materials are pulverized into a coarse powder.

2.2 Chemicals

STZ is used in this experiment and solvents like ethanol, methanol, petroleum ether, ethyl acetate, n-hexane, water, normal saline

2.3 Extraction

About 200 g of powder of *Prosopis juliflora* was packed into a soxhlet apparatus and extracted with 2 – 2.5 liters of petroleum ether at 40^0C by continuous hot percolation. The extract was subjected to distillation and it was stored on desiccators and the % yield value was determined. The same mark was continued with different organic solvents like ethyl acetate, methanol, ethanol and water according to their order of polarity.Percentage yield of extracts weredetermined.

Table 1- Extractive values of *Prosopis juliflora*

Different solvents	Percentage yield (%) (w/w)	Colour	Consistency
Petroleum ether	12%	Greenish- Black	Dry mass
n-Hexane	15%	Greenish- Black	Dry mass
Ethyl acetate	18%	Greenish- Black	Dry mass
Methanol	50%	Greenish- Black	Dry mass
Ethanol	35%	Greenish- Black	Dry mass
Water	10%	Greenish- Black	Dry mass

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2.4 Phytochemical screening

The methanolic extract of the medicinal plants were subjected to chemical test for identification.Test for alkaloids- Mayer's test, Wagner's test, Dragendroff's test, Hagner's test, Test for carbohydrates- Molisch's test, Benedict's test, Fehling's test, Test for glycosides- Modified Borntrager's test, Legal's test, Test for phytosterol-

Salkowski's test, LibermannBurchard's test, Test for saponins- Froth test, Foam test, Test for tannins- Gelatin test, Test for proteins and free amino acids- Xanthoprotein test, Ninhydrin test, Test for flavonoids- Alkaline reagent test, Lead acetate test, Shinoda test, Test for diterpenes- Copper acetate test, Test for phenols - Ferric chloride test.

2.5 Experimental Animal

Inbred Swiss albino mice of either sex of 2 months age, weighing 20±5 g, were used for the present study. The mice were obtained from the stock in breed colony. They were housed at room temperature of 23±1^{o}C, relative humidity 55±55% under 12 hr light/12 hr dark cycle in the animal house. Mice were fed with commercial pellet diet and water *ad libitum* freely throughout the study. The animals were transferred to the laboratory at least 1 hr before the start of the experiment. All animal procedures were performed after approval from the IAEC (institution of animal ethical committee) and in accordance with the recommendations for the proper care and use of laboratory animals.

2.6 Acute toxicity study

Acute oral toxicity studies was performed as per OECD-423 guidelines (acute toxic class method), with methanolic extract of *Prosopis juliflora* using albino mice (n=6) of either sex, selected by random sampling for acute toxicity study. Animals are fasted prior to dosing (e.g. without food, but with water) over-night with the mouse. Following the period of fasting, the animals should be weighed and the test substance is administered. After the substance has been administered, food may be withheld for a further. The dose level to be used as the starting dose is selected from one of four fixed levels, 5, 50, 300 and 2000 mg/kg body weight. When available information suggests that mortality is unlikely at the highest starting dose level (2000 mg/kg body weight) then, exceptionally, and only when justified by specific regulatory needs, the use of additional upper dose level of 3500 mg/kg and 5000 mg/kg body weight may be considered.

Animals are observed individually after dosing at least once during the first 30 min, periodically during the first 24 hr, with special attention given during the first 4 hr, except where they need to be removed from the study and humanely killed for animal welfare reasons are found dead. If mortality was observed in two out of three animals, then the dose administered was assigned as toxic dose. If mortality was observed in animal, then the same dose was repeated again to confirm the toxic dose, if mortality was not observed, the procedure was repeated for higher doses. As per these literature the three plants has been performed for acute toxicity with the min dose to maximum dose and finally the $ED_{50}$was calculated for the same by 1/10 of the LD_{50}.

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Table 2- Experimental protocol for the Determination of acute oral toxicity (LD_{50}) of methanolic extract of Prosopis juliflora

Name of the study	Acute toxicity
Guideline followed	OECD 423 method-acute toxic class method
Animals	Healthy young adult Swiss albino mice, nulliparous, non-pregnant
Body weight	20 ± 5 g
Sex	Either sex
Administration of dose and volume	100 and 200 mg/kg body weight, single dose in 0.5 mL
Number of groups and animals	9 groups and 6 animals in each group.
Route of administration	Oral by using mice oral feeding needle
Vehicle	Distilled water

2.7 Anti Diabetic Model

Streptozotocin-induced animal models of diabetes

Streptozotocin (STZ) is a widely used chemical for the induction of experimental diabetes in rodents. Since the initial report of its diabetogenic properties in 1963, STZ has been used alone or in combination with other chemicals or with dietary manipulations for induction of either type 1 or type 2 diabetes. Type 1 diabetes can be induced in rodents by a single STZ injection, while type 2 diabetes can be induced by at leastthree approaches, which include

STZ injection after administration of nicotinamide, high fat diet (HFD) feeding followed by a low-dose STZ injection, and STZ injection during the neonatal period. All these STZ-involved diabetic animal models have been very useful in elucidating the mechanisms of diabetic pathogenesis and in screening artificial chemicals, natural products, and pharmacological agents that are potentially capable of lowering blood glucose levels.

After two weeks of acclimatization, the diabetes was induced in rats with Streptozotocin (STZ, Sigma Chemical Company, STZ was intravenously (i.v.) administered in a dose of 40 mg/Kg dissolved in citrate buffer (0.1 M, pH 6.5). Control rats received i.v. citrate buffer. Blood glucose concentrations were measured by One Touch Ultra glucometer seven days after diabetes induction, and glucose concentrations exceeded 300 mg/dL confirmed the diabetic state.

2.8 Experimental Groups

After diabetic state was confirmed, the rats were placed in four experimental groups (n=11 animals/ group): Control rats treated with vehicle (water); Treated Control - rats treated with MEPJ extract; Diabetic diabetic rats treated with vehicle; and Treated Diabetic diabetic rats treated with MEPJ extract. The treatment dose of 400 mg/Kg/day of the MEPJ extract was orally given by gavage during 21 days. Body weight, water and food intake and blood glucose were also evaluated weekly in the morning period.

2.9 Biochemical Profile Analysis

Oral glucose tolerance test (OGTT) was performed at day 17 of treatment. After an overnight fasting of 12 hours, a glucose solution

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(200g/L) was administered into the stomach of the rats through a gastric catheter, at a final dose of 2 g/Kg body weight. The treated groups also received the plant extract 15 min. before glucose administration. Blood glucose concentrations were measured at 0 (previous administration of glucose solution/plant extract fasting glucose), 30, 60 and 120 min. Glucose responses during the OGTT were evaluated by estimation of the total area under the curve (AUC), using the trapezoidal method.At day 21 of treatment, the rats were anesthetized by sodium pentobarbital (Tiopentax® - 50 mg/Kg) and blood samples were collected by decapitation for biochemical determinations.

The blood samples were collected and put into anticoagulant free test tubes, maintained in ice for 30 min and then centrifuged at 1300×g during 10 min at 4◦C. The supernatant was collected as serum and stored at -80◦C for further determination of biochemical parameters. Serum concentrations of total protein (TP) was determined colorimetric method, and total cholesterol (CHO), triglycerides (TG), high density lipoprotein (HDL-c) concentrations; and also alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were estimated by enzymatic method (Young 2000) by Winner assay kits. The values were expressed in milligrams per deciliter (mg/dL). Very-low-density lipoprotein (VLDL) serum level estimated value was calculated through the triglyceride concentrations.

2.10 Statistical Evaluation

Analysis of variance (ANOVA) followed by Tukey's Multiple Comparison test was used to compare mean values. Differences were considered statistically significant when $p < 0.05$.

Table 3- Housing and feeding conditions for determination of acute toxicity

Room temperature	22°C ± 3°C
Humidity	40-60%
Light	12 hr : 12hr (light : dark cycle)
Feed	Standard laboratory animal food pellets with water *ad libitum*

Table 4- Study period and observation parameters for acute toxicity

Initial once observation	First 30 min and periodically 24 hr
Special attention	First 1-4 hr after drug administration
Long term observation	Up to 14 days

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Direct observation parameters	Tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma.
Additional observation parameters	Skin and fur, eyes and mucous membrane, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern etc.

3 RESULTS

Preliminary Phytochemical

The results of the preliminary phytochemical screening of the ethanolicextracts reveals the presence of phytoconstituents such as alkaloids, carbohydrates, glycosides, phytosterol, saponins, tannins, Proteins, flavonoids and diterpenes.

Acute toxicity study

As shown in Table, blood glucose levels presented near 100 mg/dL in control groups. In the diabetic groups, glucose levels were higher than 300 mg/dL. The treatment with MEPJ extract did not interfere significantly with the glycaemia of control or diabetic groups compared with their corresponding groups. The animals of control and treated groups showed no difference in body weight, water and food intake during the study. The body weight in diabetic groups was statistically lower compared to control on days 14 and 20. In addition, the plant treatment caused a reduction in the body weight compared to the diabetic group (non-treated) on days 14 and 20. The rats from diabetic groups presented higher food intake (around 30 g/day) in relation to control groups (about 16 g/day) in all experimental period. In addition, the average water intake was increasedin diabetic groups as compared to non-diabetic groups (Table 6)

Table 5- Preliminary Phytochemical screening of *Prosopis Juliflora*

S.No	Phytoconstituents	Report
1	Alkaloids	Present
2	Carbohydrates	Present
3	Glycosides	Present
4	Phytosterol	Present
5	Saponins	Present
6	Tannins	Present
7	Proteins and free amino acids	Present

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8	**Flavonoids**	**Present**
9	**Diterpenes**	**Present**

TABLE 6-Body weight, water intake and food intake on days 0, 7, 14 and 21 of the control and diabetic rats treated or not with a prosofis julifloramethanolic extract (400 mg/Kg) during 21 days of experiment.

Groups	Control	Treated Control	Diabetic	Treated Diabetic
body weight (g)				
Day 0	247.7 ± 22.1	249.0 ± 21.7	241.6 ± 19.3	231.8 ± 17.7
Day 7	253.0 ± 18.5	242.0 ± 20.3	231.5 ± 17.9	211.4 ± 26.5*
Day 14	251.9 ± 15.9	241.0 ± 22.6	229.6 ± 19.6*	207.4 ± 24.6*#
Day 20	255.8 ± 16.1	241.5 ± 19.0	230.9 ± 22.4*	208.1 ± 20.8*#
Water intake (ml)				
Day 0	37.1 ± 8.0	35.5 ± 5.3	113.6 ± 49.2*	97.1 ± 53.4*
Day 7	33.5 ± 6.1	35.0 ± 6.7	117.9 ± 55.0*	115.7 ± 55.3*
Day 14	34.6 ± 5.7	33.8 ± 6.5	137.9 ± 44.1*	123.1 ± 45.9*
Day 20	35.5 ± 4.7	33.2 ± 6.4	145.4 ± 45.5*	124.5 ± 47.5*
food intake (g)				
Day 0	17.4 ± 3.9	16.1 ± 2.8	23.6 ± 7.2	24.6 ± 8.7
Day 7	17.2 ± 3.3	17.8 ± 3.1	26.9 ± 8.3*	25.1 ± 4.8*
Day 14	17.1 ± 2.2	16.9 ± 2.5	32.1 ± 7.4*	30.2 ± 8.9*
Day 20	16.8 ± 2.0	16.9 ± 3.6	35.4 ± 8.5*	28.9 ± 8.1*

Data shown as mean± standard deviation (SD). * $p<0.05$ compared to control group (ANOVA followed Tukey's multiple comparison test). # $p<0.05$ compared to diabetic group (ANOVA followed Tukey's multiple comparison test).

As shown in Table 7, the treated control group presented HDL-cholesterol values decrease as compared to those of control group. The diabetic group presented higher levels of serum total proteins in relation to those of control group. Both diabetic groups showed higher levels of triglycerides, total cholesterol, VLDL-cholesterol concentrations, and also ALT and AST activities compared to those of control group. The treated diabetic group showed decreased HDL-cholesterol levels as compared to those of the control and diabetic groups. In addition, the plant treatment caused increased ALT and AST activities in diabetic animals compared to diabetic group.

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TABLE 7- Biochemical parameters of control and diabetic rats treated or not with a prosofis julifloramethanolic extract 400 mg/kg) during 21 days of experiment.

Groups	Control	Treated Control	Diabetic	Treated Diabetic
Total protein (g/dL)	4.3 ± 0.4	4.3 ± 0.2	5.0 ± 0.3*	4,7 ± 0,7
Triglycerides (mg/dL)	90.8 ± 27.3	121.0 ± 36.3	592.3 ± 358.6*	795.7 ±104.3*
Cholesterol (mg/dL)	81.1 ± 6.7	77.5 ± 13.7	113.0 ± 20.4*	106.7 ± 13.9*
HDL (mg/dL)	60.3 ± 8.2	26.7 ± 2.1*	61.7 ± 10.2	40.2 ± 5.7*#
VLDL (mg/dL)	17.3 ± 5.5	24.0 ± 7.3 1	18.7 ± 71.7*	159.5 ± 20.9*
ALT (U/l)	77.2 ±12.1	54.5 ± 13.9	186.7 ± 93.2*	390.0 ± 52.0*#
AST (U/l)	196.6 ± 29.6	181.0 ± 42.6	328.6 ± 146.3*	982.0 ± 151.3*#

Data shown as mean± standard deviation (SD). * $p<0.05$ compared to control group (ANOVA followed Tukey's multiple comparison test) # $p<0.05$ compared to diabetic group (ANOVA followed Tukey's multiple comparison test).

4 DISCUSSION

The estrogen affects the glucose and lipoprotein metabolism. Studies demonstrated that uncontrolled hyperglycemia, hypertension and dyslipidemia is more common in women than male with diabetes This fact explains our choice for females to evaluate the hypoglycaemic effect of MEPJ. These rats entered in the experimental design with 90 days old. In the first day of treatment, the rats were with 120 days old (adulthood). The females rats become sexually mature at 6 weeks (40 days old), and adulthood period begins after the eighth week of post-natal life (~ 60 days old), confirming that the female rats used in this study were also adult. The body weight loss represents one of the most common signs of diabetes. Despite the increased appetite, insulin deficiency reduces all anabolic processes and accelerates catabolic processes, contributing further to body weight loss, which is already occurring by glycosuria and polyuria. This status was showed in this study, since treated animals from both diabetic groups showed body weight loss, especially in the last days of treatment. The MEPJ treatment of diabetic animals led to a decreased body weight, possible due to a toxic effect of the plant in an impaired organism.

The exaggerated appetite, another physiological dysfunction caused by diabetes, is a symptom due to glucose loss in the urine at least in part, which deprives the body of a considerable part of the calories ingested with food. Large quantities of glucose are eliminated through the urine, elevating the osmotic pressure and reducing water reabsorption in the renal tubules. Due to this increased diuresis, there is excessive water intake by subject via stimulationof the thirst center in hypothalamus . The increase in water and food consumption in diabetes was confirmed in our study, and MEPJ treatment did not contribute to improve these disorders.

The blood glucose data generated from the OGTT shows that in non-diabetic rats the

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insulin uptake follows the expected physiological response, with blood glucose levels returning to its original state at the timepoint 120 min, characterizing a glycemic return. However,in non-diabetic rats treated with the plant, blood glucose level returned to the initial value already at the timepoint 60 min, which might indicate an increase in insulin release and action, resulting in a faster glucose uptake. The blood glucose level in the OGTT of diabetic rats showed that there was no reduction of the response time or the blood glucose levels of these rats. It is important to consider the diabetes type studied in this experiment. In the present study, the rats presented glycemia similar to uncontrolled human type 1 diabetes, since the Streptozotocin has a beta-cytotoxic action, leading to abnormal/lacking insulin secretion. Since there was no change in the area under the curve of Streptozotocin-induced diabetic rats, we suggest that the plant extract did not contribute to reduce the blood glucose levels.

In diabetic individuals, the lack of insulin causes inhibition of protein synthesis and increased degradation, which increases amino acid levels in the blood to be subsequently used for gluconeogenesis. Our study showed that MEPJ a treatment caused a reduction on the serum protein level. In the present study, the lipid profile of diabetic rats was abnormal as expected for diabetic patients. The triglycerides, total cholesterol and VLDL cholesterol levels were higher as compared to the nondiabetic rats due to the action of lipase, whose activity is exacerbated in individuals with reduced glucose utilization. The streptozotocin-induced diabetic animals presented a decreased insulin levels, increased triglycerides, and total cholesterol levels, corroborating with our results. Therefore, the MEPJ treatment also causes no changes in these biochemical parameters. Some studies showed a biological tendency of the HDL-cholesterol level to accompany the total cholesterol levels.

Our results showed reduced HDL-cholesterol levels in treated groups, which might indicate metabolic changes in the liver as a result of treatment, either due to reduction in its production or its function. The ALT and AST enzymes are found mainly in the hepatocytes, and when high levels are detected, it is possible to confirm the diagnosis of liver damage . Our study presented high ALT and AST activities in diabetic groups. The MEPJ treatment also caused increased activities of these enzymes, suggesting this plant led to a liver injury. This finding in association with the decreased body weight reinforce the possible toxic effect of the plant in an impaired organism by diabetes.

5 CONCLUSION

The treatment with aqueous extract of MEPJ leaves given to diabetic rats presented no hypoglycemic effect in nondiabetic animals and no antidiabetic effect in diabetic animals with the doses studied. In addition, the diabetic animals treated with the MEPJ extract caused inconvenient effects and its indiscriminate consumption requires particular carefulness.

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