Evaluation The Ameliorative Effect of Alcoholic Extracts of *Citrullus colocynthis* and *Phyllanthus Emblica* Fruits on Streptozotocin-Induced Diabetes in Male Rats

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ABSTRACT:

Diabetes mellitus (DM) is a serious health issue for the general public. In this work, male diabetic rats were used to determine the impact of Citrullus colocynthis and Phyllanthus Emblica fruits ethanolic extract (EECC and EEPE). Six groups of thirty mature rats (male Sprague Dawley) were examined. In the first group, normal rats have been fed a balanced diet served as the negative control group (C-); in the second group, diabetic rats served as the control positive (C+). Diabetic rats in groups 3, 4, 5, and 6 received daily treatments of (200 and 400 mg kg^{-1} body weight (BW) EECC and EEPE, respectively. After four weeks of treatment, Biochemical indicators were examined in all blood samples. Streptozotocin was injected and resulted in a significant reduction in feed intake (FI), feed efficiency (FER) body weight gain (BWG), serum insulin, high-density lipoprotein (HDL-c), globulin, albumin, and total protein, as well as antioxidant enzymes, glutathione (GSH) and superoxide dismutase (SOD) in pancreatic tissue, whereas a significant increment was noted in serum glucose, triglyceride (TG), total cholesterol (TC), low & very low-density lipoprotein cholesterol (LDL-c and VLDL-c), atherogenic index (AI), Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, uric acid, creatinine, tumor necrosis factor-α, creatine phosphate kinase (CPK) and lactate dehydrogenase (LDH) and lipid peroxidation (MDA) in pancreatic tissue. The treatment of diabetic animals with different ethanolic extracts caused improvements in all previously measured parameters, with EEPE (400 mg kg^{-1} BW) showing the greatest improvement.

Keywords: *Citrullus colocynthis; Phyllanthus Emblica; Blood glucose; Serum insulin*

INTRODUCTION

Diabetes mellitus is distinguished by chronic hyperglycemia and post-tprandial hyperglycemia, which both contribute to increased micro- and macrovascular morbidity and death **(Sultana *et al.*, 2014)**. DM is the most chronic illness worldwide, accounting for a substantial number of fatalities **(Niti *et al.*, 2016)**. DM is associated with protein and lipid metabolism restrictions, leading to problems such as hepatopathy, nephropathy, vasculopathy, and retinopathy **(Olotu *et al.*, 2023)**. The term DM refers to a collection of illnesses marked by insulin insensitivity and / or hyposecretion **(Al-Ahdab, 2017)**.

DM type 2 is a severe, chronic metabolic state that includes hyperglycemia, resistance to insulin, and overall insulin in the body **(Ahmed *et al.*, 2020)**. It is the most frequent kind of diabetes, accounting for 90 % of diabetic patients **(Alqahtiani *et al.*, 2020)**. Type 2 diabetes is becoming more common in most nations and is regarded as a major cause of death **(Wu *et al.*, 2014)**. It was demonstrated that streptozotocin (STZ) injection into experimental animals raises blood interleukins and TNF- levels, which promotes systemic inflammation and develops insulin resistance, all of which are essential aspects of human type 2 diabetes (**Gundala *et al.*, 2018)**.

Traditionally, phytotherapy has been commonly utilized and highly respected in the treatment of diabetes. *Citrus colocynthis* possesses anti-diabetic properties (**Ghauri *et al.*, 2020)**. *C. colocynthis'* anti-diabetic action is most likely due to its phytochemical structure. Several bioactive substances from the fruit of *C. colocynthis* have been identified in studies such as carbohydrates, flavonoids, glycosides, alkaloids, essential oils, fatty acids, and *cucurbitacins* **(Hussain *et al.*, 2014)**. The genus *Phyllanthus* (L.) belongs to the flowering plant family *Phyllanthaceae* and has over

one thousand species found worldwide. Previous research indicated that over 500 chemical substances (phyto-chemicals) have been identified from *Phyllanthus* species **(Mao *et al.*, 2016)**. *Phyllanthus Emblica officinalis* (Euphorbeaceae), sometimes known as Indian gooseberry or Amla, is a plant with medicinal properties used in the medicine of Ayurveda as well as other traditional systems. One of the most crucial components of the *E. officinalis* plant are its fruits and are used in conventional medical practices for both food and therapeutic purposes **(Prasad and Srivastava, 2021).**

This study was accomplished to evaluate the hypoglycemia impact of ethanolic extracts of *Citrus colocynthis* and *Phyllanthus Emblica officinalis* fruits on streptozotocin-induced diabetic rats to investigate its usage as an anti-diabetic herb in conventional medicine.

MATERIALS AND METHODS

Plant Material

Dry *Citrullus colo-cynthis* (*C. colocynthis*) and *Phyllanthus Emblica* (*P. Emblica*) fruits were obtained from the neighborhood supplier of herbs and medicinal plants, in Cairo, Egypt.

Extraction of Plant Material

Dry one hundred grams of powder of *C. colocynthis and P. Emblica* fruits were put in 1 L ethanol; 97%, in separate bottles, and irregularly sporadic was shaken (for three days). Then, the raw extract was filtered in filter paper (Whatman 150mm). A rotary evaporator was used to remove ethanol from the filtrate at decreased pressure and 40 °C temperature. The concentrated filtrate was stored at 4 °C until use **(Alsahli *et al.*, 2021)**.

The method required taking 100 g of powdered dry plants, namely *c. colocynthis* or *p. emblica* fruits, and combining them individually with 1 liter of 97% ethanol while shaking occasionally for 3 days. Following that, the raw extract was filtered and the

filtrate was subject to evaporation on a rotary evaporator at 40 °C and low pressure to remove the ethanol. As indicated in the work by **Alsahli *et al.* (2021)**, the concentrated filtrate was then stored at 4 °C until needed.

Drug and dose

Streptozotocin (STZ) was obtained from Al-molok Company for Chemicals, Kafr El-Sheikh, Egypt. Rats received a single intraperitoneal dosage of STZ of 65 mg kg^{-1} body weight **Ostovan *et al.* (2017)**.

Animals

Albino rats; 30 male of *Sprague Dawley* (150 ± 10 g) were acquired from the animal colony, Helwan farm, Vaccine and Immunity Organization, Ministry of Health, Cairo, Egypt.

Induced diabetes for rats

To induce diabetes in male rats, they were intraperitoneally injected with STZ at a single dosage of 65 mg kg^{-1} of body weight after night fasting. All the injected rats were provided access to water and food. Blood glucose levels were assessed three days after STZ injections to verify that diabetes had been induced in the animals. Diabetic rats were those with blood glucose levels of more than 300 mg dl^{-1}. Healthy rats were also examined for their glucose levels **(Ostovan *et al.*, 2017)**.

Experimental Design and animal groups

A total of thirty adult male rats weighing around 150 ± 10 g, were kept in hygienic cages. Prior to the experiment, these rats were given a week to adapt to their surroundings. They were provided with a well-balanced diet based on **Reeves et all's (1993)** recommendations. The rats were separated into six groups (each one has five rats (n=5)), for the purpose of the experiment.

Group 1 consisted of normal rats that were given a balanced diet and served as the negative control (-).

Group 2 was a positive control (+), consisting of

diabetic rats that were also given a balanced diet.

Groups 3 and 4 comprised diabetic rats receiving daily treatment of 200 and 400 mg kg^{-1} BW of ethanolic extract of *C. colocynthis* fruits (EECC) (**Jayaraman *et al.*, 2009)**.

Group (5) and (6): Rats with diabetes in those groups were administered the ethanolic extract of *P. emblica* fruits (EEPE) at 200 and 400 mg kg^{-1} daily dosage of body weight, respectively **(Al-Ahdab, 2017)**.

Determination of the chemical composition of plant materials

The protein, fat, moisture, fiber, and ash content will be analyzed using the **A.O.A.C (2000)** methods, while the total carbohydrate will be determined through the following calculation: Carbohydrates % = 100 - (moisture % + protein % + fat % + ash %+fiber).

Biological evaluation

Weekly measurements were taken for body mass and food consumption, and the total food intake for the study time (four weeks) was calculated using the method described by **Chapman *et al.* (1959).** The feed efficiency ratio was determined following the equation provided by **Hosoya (1980)**.

FER =Body weight gain (g) / feed intake (g) during the experimental period.

Biochemical analysis of serum

Trinder's (1969) method was used to determine the blood glucose levels, while the method by **Yallow and Bauman (1983)** was employed to estimate the serum insulin levels. HOMA-IR and HOMA-*B* were calculated by the next equation: HOMA-IR = [fasting insulin (μU ml^{-1}) ×fasting plasma glucose (mg dl)]/405; HOMA-*B*= (360×fasting insulin (μU ml^{-1})/ [fasting plasma glucose (mg dl^{-1}) – 63] **(Matthews *et al.*, 1985)**.

Richmond's (1973) method was used for chemically determining total cholesterol (TC), while

Trinder and Ann's (1969) method was used for measuring triglycerides (TG). A diagnostic kit for measuring high-density lipoprotein cholesterol (HDL-C) using spectrophotometry was determined by **Richmond (1973)**. Moreover, LDL-c and VLDL-c concentrations were assessed by the next equations according to **Friedewald *et al.*, (1972)**:

VLDL-C (mg/dl) = TG (mg/dl)/5

LDL-C = TC – [(HDL-C) + (VLDL-C)]

The atherogenic inde**x** was determined by the next equation:

AI = LDL.C / HDL.C **(Kumari *et al.*, 1995)**

Serum ALT and AST were evaluated by **Bergmeyer *et al.* (1978)**, while alkaline phosphatase (ALP) was determined by **Roy (1970)**. **Sonnenwirth and Jaret (1980); Drupt's (1974)** methods were used to determine total protein and albumin, respectively, while serum globulin was estimated according to **(Chary and Sharma, 2004)**. Blood urea nitrogen was determined as in **(Patton and Crouch, 1977)**, while the enzymatic colorimetric technique was used to assess serum uric acid **(Fossati *et al.*, 1980)**. **Husdan and Rapoport's (1968)** method was used to determine serum creatinine conce-ntrations. Finally, **Campbell's (1997)** method was used to measure the level of tumor necrosis factor-α. The enzymatic functions of lactate dehydrogenase (LDH) and creatine phosphate kinase (CPK) were ultimately evaluated utilizing the methodology outlined in **Horder *et al.* (1991); Weishaar (1975)** respect-tively.

Antioxidant biomarker

The levels of malondialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH) as indications of oxidative stress were measured in the homogenized pancreas (**Yoshioka *et al.*, 1979))**; **Giannopolitis and Ries, 1977; Beutler *et al.*, 1963)**.

Statistical analysis

The process of statistical analysis involved utilizing the one-way analysis of variance, the ANOVA test, then the Duncan test, by version 16 of the Statistical Packages for the Social Science (SPSS) (v. 16) software. The resulting data were presented in the form of mean ± SD. The dissimilarities between means were significant at $p < 0.05$ as per **Snedecor and Cochran's (1989)** analysis.

Results

According to the findings presented in **Table 1**, the chemical examination of the dried *C. colocynthis* and *P. Emblica* fruits. *P. Emblica* showed the highest carbohydrate value (77.37 ± 1.00) followed by *C. colocynthis* (32.63 ± 1.00). While the highest fiber, fat, protein, and ash values were noted for *C. colocynthis* as (41.12 ± 1.00), (10.48 ± 1.00), (8.62 ± 1.40) and (7.15 ± 1.00) respectively, followed by *P. Emblica* (17.08 ± 1.00), (0.00 ± 0.00), (1.94 ± 1.00) and (4.17 ± 1.00) respectively.

The changes in FI, BWG %, and feed efficiency ratio (FER) in control and experimental rats are displayed in **Table (2)**. These parameters declined in diabetic (+) control, whereas, they enhanced in treated groups, especially with high dosages. The most recorded improvements were observed in the treated group with EEPE (400 mg kg^{-1} BW), the percentage of change in FI, BWG) % and FER from positive control was (-16.49, -148 & -113.95 respectively) and then in the treated group with EECC (400 mg kg^{-1} BW).

Data displayed in **Table (3)** represent the influence of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on blood glucose and serum insulin of diabetic animals. It may be seen and noted that the mean values of glucose of (+) control were greater than (-) one, being 418.33±1.50 and 80.33±1.09 (mg dl^{-1}) respectively. The best data of serum glucose was noticed for

animals treated with (EEPE 400 mg kg^{-1} BW) than the other animals treated and the (+) control. The decrease in serum glucose was 69.40%.

The average value of serum insulin significantly declined in the (+) control than in the (-) control. All treated groups exhibited a significant increment to the (+) control. The best data was recorded in the rats that were treated with EEPE (400 mg kg^{-1}). The increase in serum insulin was -221.65%.

The mean values of homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta-cell function (HOMA-*B*) are displayed in Table (4). It may be noted that the average values of (HOMA-IR) of the (+) control were higher than the (-) one (2.36 ± 0.31 and 1.54 ± 0.17 respectively) which indicated that the group has insulin resistance compared to the normal group which induced type 2 of diabetes. Furthermore, it may be observed that the average values of (HOMA-*B*) of the (+) control group were lower than the (-) one. All treated rats have shown insignificant increment in (HOMA-*B*) than the diabetic rats. The best data was obtained in treating diabetic rats with EEPE (400 mg kg^{-1}), which recorded an increase in (HOMA-*B*) as -1670.21%.

Data in **Table (5)** present the influences of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on TC and TG of diabetic groups. It may be noticed that the average values of TC and TG in the (+) control group were greater than the (-) control. All treated rats revealed significantly lessening in TC and TG in serum than the diabetic rats. The best results were noted in treating diabetic rats with EEPE (400 mg kg^{-1}) then by EECC (400 mg kg^{-1}), then the other treated rats, and the (+) control.

Table (6&7) shows the influences of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on serum VLDL-c, HDL-c, LDL-c, and AI of diabetic animals. It may

be noticed that the average values of VLDL-c, of the (+) control group was greater than the (-) control. All treated diabetic rats with the two ethanolic extracts encouraged a significant decline in VLDL-c than the (+) control. In contrast, insignificant change in VLDL-c was recorded in higher dosages of treated rats with EEPE and EECC (400 mg kg^{-1} BW).

It might be demonstrated that the average HDL-c values of the (-) control were greater than the (+ve) control. The best data of HDL-c was shown for treated rats with higher dosages of EEPE and EECC (400 mg kg^{-1} BW) which revealed a highly significant increment in the average value of serum HDL-c than the (+) control as in **Table (6),** which recorded an increase in HDL-c as -54.75%.

In this table, it is also indicated that the average values of LDL-c and AI of the (-) control were smaller than the (+) control. All of these parameters improved in treated rats with the best serum LDL-c and AI results were shown in the group treated with EEPE (400 mg kg^{-1} BW). Which recorded a decrease in LDL-c was 88.23%.

The average values of ALT, AST, and ALP in the (+) control showed a significant increase in the (-) control. All liver enzymes decreased significantly in all treated rats than diabetic ones. The best results of these parameters were noticed in rats that received EEPE (400 mg kg^{-1} BW) which recorded a decrease in ALT, AST, and ALP as (59.74%, 47.97%, and 34.73%) respectively than that received EECC (400 mg kg^{-1} BW).

The results revealed that there was a significant decrease in the average values of total protein, albumin, and globulin in the diabetes control than in the normal control. While all treated diabetic rats noticed a significant increase compared to the (+) control. The treated group with EEPE and EECC had the highest level of total protein and globulin (400 mg kg^{-1} BW), but there was an insignificant difference

between them. The strongest result in albumin was achieved in the treated group with EEPE (400 mg kg^{-1} BW), which is apparent in **(Table.9)**.

In Table 10, it was obvious that there were significant variations in urea, uric acid, and creatinine levels among the (+) control set and all groups. Specifically, the positive control exhibited a significant rise in urea, uric acid, and creatinine than the negative control. The most favorable outcomes were observed in the groups treated with EEPE (400 mg kg-1) recording a decrease in urea, uric acid, and creatinine levels as (69.17%, 34.38%, and 59.73%) respectively, then with EECC (400 mg kg^{-1}) respectively.

Data in **Table (11**) cleared that the (+) control showed a significant increase in Tumor necrosis factor-α and lactate dehydrogenase compared to the (-) control, while all handled groups showed a significant decrease in Tumor necrosis factor-α and lactate dehydrogenase compared to the positive control group. The best data obtained for groups treated with EEPE (400mg/kg) that a achieved Percentage decrease in Tumor necrosis factor-α and lactate dehydrogenase were (57.82% and 40.23%), followed by the treated group with EECC (400mg/kg).

In this table, it was also found that the (+) control recorded a significant increment in creatine phosphate kinase compared to all treated groups as well as the (-) group. There was no significant difference between the normal group and the group treated with EEPE (400mg/kg) which achieve a decrease in this parameter achieving a decrease in creatine phosphate kinase at 37.54%.

The result in **Table (12)** exhibited that diabetic control recorded a highly significant increase in MDA (20.26 ± 1.19) compared to normal control (5.52 ± 0.60). Whereas, treated rats achieved a significant decline in MDA. The nearby results for the normal group were got in-group treated with EEPE (400

mg kg^{-1}) and then in groups treated with EECC (400 mg kg^{-1}). The decrease percentage was 57.65% and 52.71 respectively.

It may be noted that the average values of reduced GSH of (-) control was higher than (+) control. The highest GSH average was shown for the group treated with 400 mg kg^{-1} EEPE and EECC compared to other groups and (+) control. Furthermore, data in **Table (12)** showed that the average values of SOD in (-) control were higher than in (+) control; (133.75 ± 5.35) and (62.75 ± 2.95) respectively. The favorable results of SOD were significantly shown in the group treated with EEPE (400 mg kg^{-1}) where SOD increased than in the other treated groups, the (+) control and the average value was close to the normal group.

DISCUSSION

Various preparations of *C. Colocynthis* contained proteins, carbohydrates, distinct amino acids, tannins, steroids, alkaloids, phenolic compounds, terpenoids, glycosides, and cucurbitacin's a, b, c, d, e, j, and l, as reported by **Mazher *et al.* (2020)**. *P. emblica*, on the other hand, is abundant in vitamin C, proteins, carbohydrates, minerals, fiber, and potent polyphenols such as gallic acid, as stated by **Thangachi *et al.* (2022)**.

The present results are accorded with **Gupta *et al.*, (2012)** who stated that STZ-induced diabetic rats revealed signs of weight loss than non-injected rats. As well, these results are in accord with further experimentations of **Makinde *et al.*, (2020); Aksu *et al.*, (2021) who** showed a significant reduction in diabetic rats' body weight.

The present study achieved a similar result to **Kumar *et al.*, (2012)** who stated a marked elevation in plasma glucose content and a decline in insulin levels in rat STZ-injected. **Ebrahimi *et al.*, (2016)** revealed that the hydro-alcoholic extract of *C. colocynthis* leaves showed effective antihyperglycemic and antihyperlipidemic effects such as lower fasting blood

sugar, LDL-c, TC, ALT, AST, creatinine, urea, TG, and bilirubin concentrations in rats with diabetes to whom it was given. Additionally, **Ghauri *et al.*, (2020)** found that the hydro-ethanolic soft surface of *C. colocynthis* has an antihyperglycemic consequence in diabetic rats at the dosage of 300 mg kg^{-1} where it decreased their blood glucose and triglyceride, and cholesterol contents. Also, in vitro examination, *C. colocynthis* impeded gluco-sidase, which is accountable for postprandial hyperglycemia. The decline in the serum level of glucose to normal level in the treated rats could be associated with incomplete regeneration or preserving the pancreatic B-cell weight by *C. colocynthis* in diabetic rats induced by STZ **(Sebbagh *et al.*, 2009)**. When insulin signaling is disrupted, insulin resistance develops. At first, this resistance is overcome by increasing insulin release, but then, the amount of insulin released by pancreatic beta-cells is not enough to maintain a normal blood glucose level, which results in T2D **(Alqudah *et al.*, 2023)**.

In the study of **Snehal *et al.*, in 2013**, it was referred to that the administration of STZ resulted in the development of a diabetic state in rats, characterized by several typical symptoms including weight loss, excessive thirst, sugar in the urine, increased appetite, reduced insulin levels, and high blood sugar levels, along with elevated cholesterol and triglycerides. However, treatment with a hydro-alcoholic extract of *P. emblica* fruits was found to prevent these symptoms and significantly reduce fasting serum glucose, cholesterol, triglyceride, LDL-C, and very VLDL-C levels in diabetic rats. Conversely, insulin and HDL-C levels were insignificantly influenced by the treatment. Additionally, the treatment also showed a decrease in lipid peroxidation and an elevation in antioxidant activity in the liver of diabetic rats. Another study by **Ahmed (2017)** demonstrated that an

aqueous extract of *P. emblica* resulted in significant enhancements in serum glucose levels, liver enzymes, lipid profile, and kidney function in overweight rats.

In this work, the results are matched with the previous results of **Ebrahimi *et al.*, (2016)** who noticed a significant increase in the levels of TC, TG, and LDL-c and a noticeably decreasing in serum level of HDL-c where the STZ-induced diabetic rats.

Gill *et al.*, (2011) observed a significant decrease in AST, ALT activities, as well as serum albumin. Furthermore, blood creatinine and urea levels in diabetic rats that were treated with *C. colocynthis* leaf extract were less than in untreated ones with diabetes. These benefits might be attributed to *C. colocynth is* anti-oxidant properties since it has been discovered that this plant can enhance antioxidant enzymes such as GSH, SOD, and GPX. Furthermore, earlier research has demonstrated that a hydro-alcoholic extract of *C. colocynthis* improves liver tissue and promotes beta-cell renewal **(Afifi-Yazar *et al.*, 2011)**. Our results were also similar to **Omayma *et al.*, (2013)** who found a significant decline in blood glucose, urea, uric acid, creatinine, TC, TG, LDL-C, MDA concentrations, AST, ALT activity with a considerable increase in GSH level and SOD activity of diabetic rats handled with *citrullus colocynthis* compared to diabetic rats. **Bagherizadeh *et al.*, (2015)** stated that *C colocynthis* pulp led to the decreasing serum level of uric acid, urea, and creatinine in diabetic animals.

The current findings also were close to **Akhtar *et al.*, (2011) who** reported that *P. emblica* treatment had a significant decline in TC, LDL-C, and TG, as well, as a significant rise in HDL-C. **Sarvaiya *et al.*, (2015)** reported that gouty rats administrated with 200 and 400 mg kg^{-1} body weight of *P. emblica* aqueous extract and administrated with 200 and 400 mg kg^{-1} body weight of *P. emblica* alcoholic extracts reduced the creatinine, uric

acid, and BUN levels in serum than rats of the gout control group. **Purena *et al.*, (2018)** investigated the protective action in cisplatin-induced nephrotoxicity rats treated with *P. emblica* hydro-ethanolic leaves extract and conducted that treating with (200 and 400 mg kg) dosages of P. *Emblica* leaves extract significantly decreased the serum creatinine and urea nitrogen, as well it improved the catalase, SOD and GPx activities.

The results also are similar to those of **Bhandari and Ansari, (2009),** who concluded a significant increase in blood glucose, serum CK, and serum LDH in STZ-induced diabetic rats, while they recorded decreasing in SOD, CAT, and GSH concentrations compared to normal rats. **Sanadgol *et al.* (2011)** conducted that the extract of *C. colocynthis* exhibited a significant reduction in the expression of TNF-α in fat mice when measuring TNF-α serum levels. Similarly, **Manzoor *et al.* in 2022** examined the cardioprotective effect of the hydro-alcohol peel extracts of *C colocynthis linen*. The results showed that the groups treated with these extracts experienced a noteworthy decrease ($P < 0.001$) in ALT, ALP, AST, lactate dehydrogenase, and creatinine-kinase levels.

Tiwari *et al.*, (2011) stated that *P. emblica* extract could significantly hinder the TNF-α expression in diabetic rats' serum **Girsang and Melinda, (2021)** indicated that *P. emblica L*. fruits extract comprises tannins, alkaloids, terpenoids, flavonoids, phenolics, and triterpenoids substances. A 400 mg kg^{-1} BW dosage of this extract displayed the best decline in CK-MB concentrations with great enhancements of heart tissues, this result agreed with this study. The present results were confirmed by **Adedara *et al.*, (2019); Zhou, (2020)** who found also a significant decrease in GSH in diabetic rats. *C. colocynthis* administration also declined MDA contents and increased GSH as reported by

Mohammad Zadeh and Gol, (2022). These results agreed with **Patel and Goyal, (2011),** where the oral administration with *P. emblica* juice reduced serum activity levels of LDH, MDA, creatine kinase-MB, and, while significantly increased the levels of catalase, SOD, and GSH.

CONCLUSION

Based on the findings, the current research demonstrated that the ethanolic extracts of *Citrullus colocynthis* and *Phyllanthus embolic*a fruits have a noteworthy anti-hyperglycemic effect and can enhance the body's vital functions.

Recommendation: It is a worthy trial to use *Citrullus colocynthis* and *Phyllanthus emblica* fruits as drinks for patients after clinical trials of diabetes may help the medical treatment.

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Table (1): Chemical analysis of dry *C. colocynthis* and *P. Emblica* fruits (average ± SD)

Components %	*C. colocynthis*	*P. Emblica*
Carbohydrate	32.63 ± 1.00[b]	**77.37 ± 1.00[a]**
Protein	8.62 ± 1.40[d]	**1.94 ± 1.00[d]**
Fat	10.48 ± 1.00[c]	**0.00 ± 0.00[e]**
Fiber	41.12 ± 1.00[a]	**17.08 ± 1.00[b]**
Ash	7.15 ± 1.00[d]	**4.17 ± 1.00[c]**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (2): Effect of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on feed intake, body weight gain, and feed efficiency ratio of diabetic rats (average ± SD, n=5)

Parameters / Groups	FI (g per 28 days)	% change vs (+control)	BWG (%)	% change vs (+control)	FER	% change vs (+control)
Normal (-control)	574.20 ± 0.34[a]	20.28	43.82 ± 3.70[a]	217.54	0.114 ± 0.00[a]	165.12
Diabetic (+control)	477.40 ± 1.40[d]	-	13.80 ± 1.76[e]	-	0.043 ± 0.00[e]	-
Diabetic + EECC (200 mg kg^{-1})	526.26 ± 0.23[c]	10.23	20.05 ± 0.46[d]	45.29	0.057 ± 0.00[d]	32.56
Diabetic + EECC (400 mg kg^{-1})	553.00 ± 0.21[b]	15.84	32.02 ± 2.85[b]	132.03	0.087 ± 0.01[b]	102.33
Diabetic + EEPE (200 mg kg^{-1})	526.44 ± 0.51[c]	10.27	26.27 ± 0.40[c]	90.36	0.074 ± 0.00[c]	72.09
Diabetic + EEPE (400 mg kg^{-1})	556.13 ± 1.80[b]	16.49	34.36 ± 1.25[b]	148.99	0.092 ± 0.00[b]	113.95

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (3): Effects of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on blood glucose and serum insulin levels of diabetic rats (average ± SD, n=5)

Parameters / Groups	blood glucose (mg dl^{-1})	% change vs (+ control)	serum insulin (µU ml^{-1})	% change vs (+ control)
Normal (-control)	80.33 ± 1.09^{e}	-80.80	7.78 ± 0.43^{a}	**236**
Diabetic (+control)	418.33 ± 1.50^{a}	-	2.31 ± 0.17^{e}	**-**
Diabetic + EECC (200 mg kg^{-1})	380.00 ± 0.80^{b}	-9.16	3.51 ± 0.23^{d}	**51.94**
Diabetic + EECC (400 mg kg^{-1})	156.00 ± 3.38^{d}	-62.71	6.96 ± 0.52^{b}	**201.29**
Diabetic + EEPE (200 mg kg^{-1})	227.50 ± 2.51^{c}	-45.62	4.70 ± 0.18^{c}	**103.46**
Diabetic + EEPE (400 mg kg^{-1})	128.00 ± 1.10^{d}	-69.40	7.43 ± 0.40^{ab}	**221.65**

Averages in the same column with fully diverse letters are significantly different at p<0.05

Table (4): Effects of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on HOMA-IR and HOMA-*B* levels of diabetic rats (average ± SD, n=5)

Parameters / Groups	HOMA-IR	% change vs (+ control)	HOMA-*B*	% change vs (+ control)
Normal (-control)	1.54 ± 0.17^{c}	-35.56	220.82 ± 0.35^{a}	**9295.7**
Diabetic (+control)	2.39 ± 0.15^{b}	-	2.35 ± 0.01^{b}	**-**
Diabetic + EECC (200 mg kg^{-1})	3.29 ± 0.19^{a}	37.66	3.99 ± 0.01^{b}	**69.78**
Diabetic + EECC (400 mg kg^{-1})	2.67 ± 0.56^{b}	11.72	30.76 ± 0.25^{b}	**1208.94**
Diabetic + EEPE (200 mg kg^{-1})	2.64 ± 0.25^{b}	10.46	10.47 ± 0.05^{b}	**345.53**
Diabetic + EEPE (400 mg kg^{-1})	2.36 ± 0.31^{b}	-1.26	41.60 ± 0.02^{b}	**1670.21**

Averages in the same column with fully diverse letters are significantly different at p<0.05

Table (5): Effect of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on total cholesterol (TC) and triglycerides (TG) of diabetic rats (average ± SD, n=5)

Parameters / Groups	TC (mg dl^{-1})	% change vs (+ control)	TG (mg dl^{-1})	% change vs (+ control)
Normal (-control)	65.60 ± 0.91^{d}	-46.74	73.00 ± 1.56^{e}	**-46.91**
Diabetic (+control)	123.16 ± 0.05^{a}	-	137.50 ± 0.50^{a}	**-**
Diabetic + EECC (200 mg kg^{-1})	108.36 ± 0.18^{b}	-12.02	123.50 ± 1.50^{b}	**-10.18**
Diabetic + EECC (400 mg kg^{-1})	76.03 ± 2.89^{cd}	-38.27	94.33 ± 0.35^{d}	**-31.39**
Diabetic + EEPE (200 mg kg^{-1})	83.40 ± 0.50^{c}	-32.28	107.00 ± 0.54^{c}	**-22.18**
Diabetic + EEPE (400 mg kg^{-1})	72.86 ± 2.92^{cd}	-40.84	86.00 ± 2.00^{d}	**-37.45**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (6): Effects of ethanolic extracts of *C. colocynthis* and *P. Emblica* fruits on serum lipoprotein cholesterol (VLDL-c) and (HDL-c) of diabetic rats (average ± SD, n=5)

Parameters / Groups	VLDL-c (mg dl^{-1})	% change vs (+ control)	HDL-c (mg dl^{-1})	% change vs (+ control)
Normal (-control)	14.60 ± 1.11^{e}	-46.91	48.33 ± 1.15^{a}	**72.61**
Diabetic (+control)	27.50 ± 1.70^{a}	-	28.00 ± 1.00^{e}	**-**
Diabetic + EECC (200 mg kg^{-1})	24.70 ± 0.30^{b}	-10.18	33.00 ± 2.00^{d}	**17.86**
Diabetic + EECC (400 mg kg^{-1})	18.86 ± 1.27^{d}	-31.42	43.50 ± 0.50^{b}	**55.36**
Diabetic + EEPE (200 mg kg^{-1})	21.40 ± 1.50^{c}	-22.18	38.00 ± 1.00^{c}	**35.71**
Diabetic + EEPE (400 mg kg^{-1})	17.20 ± 0.80^{d}	-37.45	43.33 ± 2.08^{b}	**54.75**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (7): Effects of ethanolic extracts of *C. colocynthis* and *P. Emblica* fruits on serum lipoprotein cholesterol (LDL-c) and atherogenic index (AI) of diabetic rats (average ± SD, n=5)

Parameters / Groups	LDL-c (mg dl^{-1})	% change vs (+ control)	AI	% change vs (+ control)
Normal (-control)	2.66 ± 0.57^{e}	-96.07	0.055 ± 0.01^{d}	**-97.72**
Diabetic (+control)	67.66 ± 1.80^{a}	-	2.413 ± 0.16^{a}	**-**
Diabetic + EECC (200 mg kg^{-1})	50.66 ± 1.40^{b}	-25.13	1.536 ± 0.30^{b}	**-36.34**
Diabetic + EECC (400 mg kg^{-1})	13.66 ± 2.08^{d}	-79.81	0.314 ± 0.05^{d}	**-86.98**
Diabetic + EEPE (200 mg kg^{-1})	24.00 ± 3.60^{c}	-64.53	0.631 ± 0.09^{c}	**-73.85**
Diabetic + EEPE (400 mg kg^{-1})	12.33± 0.57^{d}	-81.78	0.284 ± 0.01^{d}	**-88.23**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (8): Effects of ethanolic extracts of *C. colocynthis* and *P. Emblica* fruits on liver function (ALT), (AST) and (ALP) of diabetic rats (average ± SD, n=5)

Parameters / Groups	ALT (U L^{-1})	% change vs (+ control)	AST (U L^{-1})	% change vs (+ control)	ALP (U L^{-1})	% change vs (+ control)
Normal (-control)	14.00 ± 1.00^{e}	-72.28	72.00 ± 3.00^{e}	-53.94	242.50 ± 0.85^{e}	**-46.70**
Diabetic (+control)	50.50 ± 1.50^{a}	-	156.33 ± 6.50^{a}	-	455.00 ± 1.20^{a}	**-**
Diabetic + EECC (200 mg kg^{-1})	43.50 ± 2.50^{b}	-13.86	111.33 ± 4.96^{b}	-28.79	411.50 ± 1.45^{b}	**-9.67**
Diabetic + EECC (400 mg kg^{-1})	28.66 ± 0.31^{c}	-43.25	95.33 ± 0.52^{c}	-39.02	363.50 ± 2.50^{c}	**-20.11**
Diabetic + EEPE (200 mg kg^{-1})	34.00 ± 3.00^{c}	-32.67	98.50 ± 1.50^{c}	-36.99	376.00 ± 1.10^{c}	**-17.36**
Diabetic + EEPE (400 mg kg^{-1})	20.33 ± 1.80^{d}	-59.74	81.33 ± 1.52^{d}	-47.97	297.00 ± 1.90^{d}	**-34.73**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (9): Effects of ethanolic extracts of *C. colocynthis* and *P. Emblica* fruits on serum total protein, albumin (Alb), and globulin (Glob) of diabetic rats (average ± SD, n=5)

Parameters / Groups	TP (g dl^{-1})	% change vs (+ control)	Alb (g dl^{-1})	% change vs (+ control)	Glob (g dl^{-1})	% change vs (+ control)
Normal (-control)	8.39 ± 0.02^{a}	67.13	4.72 ± 0.03^{a}	72.26	3.67 ± 0.02^{a}	**60.96**
Diabetic (+control)	5.02 ± 0.08^{e}	-	2.74 ± 0.03^{f}	-	2.28 ± 0.05^{d}	-
Diabetic + EECC (200 mg kg^{-1})	6.65 ± 0.21^{d}	32.47	3.25 ± 0.12^{e}	18.61	3.40 ± 0.10^{c}	**49.12**
Diabetic + EECC (400 mg kg^{-1})	7.72 ± 0.22^{b}	53.78	4.18 ± 0.17^{c}	52.55	3.54 ± 0.07^{b}	**55.26**
Diabetic + EEPE (200 mg kg^{-1})	6.91 ± 0.08^{c}	37.64	3.52 ± 0.06^{d}	28.47	3.39 ± 0.03^{c}	**48.68**
Diabetic + EEPE (400 mg kg^{-1})	7.92 ± 0.10^{b}	57.77	4.37 ± 0.08^{b}	59.49	3.55 ± 0.01^{b}	**55.70**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (10): Effects of ethanolic extracts of *C. colocynthis* and *P. Emblica* fruits on serum uric acid, creatinine, and blood urea nitrogen of diabetic rats (average ± SD, n=5)

Parameters / Groups	Urea (mg dl^{-1})	% change vs (+control)	Uric acid (mg dl^{-1})	% change vs (+control)	Creatinine (mg dl^{-1})	%change vs (+control)
Normal (-control)	15.00 ± 0.95^{e}	-82.91	1.95 ± 0.15^{e}	-44.13	0.41 ± 0.01^{e}	**-72.48**
Diabetic (+control)	87.75 ± 1.20^{a}	-	3.49 ± 0.02^{a}	-	1.49 ± 0.10^{a}	-
Diabetic + EECC (200 mg kg^{-1})	70.16 ± 1.82^{b}	-20.05	3.26 ± 0.07^{b}	-6.59	1.19 ± 0.19^{b}	**-20.13**
Diabetic + EECC (400 mg kg^{-1})	45.85 ± 2.35^{c}	-47.75	2.81 ± 0.05^{c}	-19.48	0.85 ± 0.02^{c}	**-42.95**
Diabetic + EEPE (200 mg kg^{-1})	52.83 ± 1.54^{c}	-39.79	2.99 ± 0.20^{c}	-14.33	0.95 ± 0.03^{c}	**-36.24**
Diabetic + EEPE (400 mg kg^{-1})	27.05 ± 1.25^{d}	-69.17	2.29 ± 0.11^{d}	-34.38	0.60 ± 0.02^{d}	**-59.73**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

Table (11): Effect of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on tumor necrosis factor-α, creatine phosphate kinase (CPK), and lactate dehydrogenase (LDH) of diabetic rats (average ± SD, n=5)

Parameters / Groups	TNF- α (pg ml^{-1})	%change vs (+control)	CPK (U L^{-1})	%change vs (+control)	LDH (U L^{-1})	% change vs (+control)
Normal (-control)	18.50 ± 1.99^{e}	-68.56	717.33 ± 3.89^{e}	-47.81	993.00 ± 4.00^{e}	**-45.64**
Diabetic (+control)	58.85 ± 2.45^{a}	-	1374.50 ± 2.65^{a}	-	1826.66 ± 1.51^{a}	**-**
Diabetic + EECC (200 mg kg^{-1})	47.56 ± 1.74^{b}	-19.18	1236.50 ± 3.41^{b}	-10.04	1644.66 ± 1.62^{b}	**-9.96**
Diabetic + EECC (400 mg kg^{-1})	26.67± 2.77^{d}	-54.68	909.67 ± 1.35^{d}	-33.82	1180.00 ± 2.57^{d}	**-35.40**
Diabetic + EEPE (200 mg kg^{-1})	38.00 ± 1.80^{c}	-35.43	1094.00 ± 5.17^{c}	-20.41	1456.67 ± 5.42^{c}	**-20.26**
Diabetic + EEPE (400 mg kg^{-1})	24.82 ± 2.17^{d}	-57.82	821.50 ± 4.50^{de}	-40.23	1141.00 ± 1.13^{d}	**-37.54**

Averages in the same column with fully diverse letters are significantly different at p<0.05

Table (12): Effect of ethanolic extract of *C. colocynthis* and *P. Emblica* fruits on antioxidant enzymes (GSH & SOD) and lipid peroxidation (MDA) in pancreas tissue of diabetic rats (average ± SD, n=5)

Parameters / Groups	MDA (nmol g^{1})	%change vs (+control)	GSH (mmol g^{-1})	% change vs (+control)	SOD (U g^{-1})	% change vs (+control)
Normal (-control)	5.52 ± 0.60^{e}	-72.75	2.14 ± 0.07^{a}	319.61	133.75 ± 5.35^{a}	**113.15**
Diabetic (+control)	20.26 ± 1.19^{a}	-	0.51 ± 0.03^{e}	-	62.75 ± 2.95^{e}	**-**
Diabetic + EECC (200 mg kg^{-1})	17.05 ± 1.24^{b}	-15.84	0.86 ± 0.10^{d}	68.63	77.05 ± 2.05^{d}	**22.79**
Diabetic + EECC (400 mg kg^{-1})	9.58 ± 1.16^{d}	-52.71	1.74 ± 0.11^{b}	241.18	115.30 ± 1.50^{b}	**83.75**
Diabetic + EEPE (200 mg kg^{-1})	14.10 ± 0.42^{c}	-30.40	1.26 ± 0.07^{c}	147.06	99.30 ± 5.60^{c}	**58.25**
Diabetic + EEPE (400 mg kg^{-1})	8.58 ± 1.13^{d}	-57.65	1.86± 0.11^{b}	264.71	125.13 ± 4.02^{ab}	**99.41**

Averages in the same column with fully diverse letters are significantly different at p<0.05.

تقييم الدور المحسن للمستخلصات الكحولية لثمار نباتي الحنظل والأملج على داء السكري المستحث بالستربتوزوتوسين في ذكور الجرذان

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المستخلص العربي

مرض السكري يعد مشكلة صحية عامة لذلك تهدف هذه الدراسة إلى تقييم تأثير المستخلص الإيثانولي لثمار نباتي الحنظل والأملج على ذكور الفئران المصابة بالسكري حيث تم تقسيم ثلاثون فأرمن الذكور البالغين سبراجي دولي إلى ست مجموعات. المجموعة (1): هي جرذان سليمة تتغذى على الغذاء المتوازن كمجموعة ضابطة سالبة(-C) ، المجموعة (2): هي المجموعة الضابطة الموجبة (+ C) (الجرذان المصابة بالسكر). المجموعة (3) و (4) و (5) و (6) الجرذان المصابة بالسكر وتعالج يوميا بتركيزين (200 و400 ملجم لكل كجم من وزن الجسم) لكل من المستخلص الإيثانولي لنباتي الحنظل والأملج على التوالي. في نهاية التجربة، بعد 28 يومًا من العلاج، تم تقدير الاختبارات البيوكيميائية للدم. وأوضحت النتائج أن الحقن بالستربتوزوتوسين سبب انخفاض معنوي في المأخوذ الغذائي، ووزن الجسم المكتسب، ومعدل كفاءة الغذاء، والكوليسترول المرتبط بالليبوبروتين مرتفع الكثافة، والبروتين الكلي، والألبومين والجلوبيولين في السيرم والإنزيمات المضادة للأكسدة (الجلوتاثيون و السوبر أكسيد ديسميوتيز) في أنسجة البنكرياس بينما تم تسجيل زيادة كبيرة في مستوي الجلوكوز ، والكوليسترول الكلي ، والدهون الثلاثية ، والكوليسترول المرتبط بكل من الليبوبروتين منخفض الكثافة و الليبوبروتين شديد إنخفاض الكثافة ، مؤشر تصلب الشرايين ، و الأسبارتات أمينوترانسفيراز ، والألانين أمينو ترانسفيراز ، والفوسفاتاز القلوي ، و اليوريا ، و حمض البوليك، و الكرياتينين، و عامل النخر ألفا، و الكرياتين فوسفات كيناز ، و إنزيم اللاكتات ديهيدروجينيز في السيرم وبيروكسيد الدهون في أنسجة البنكرياس. أظهرت الجرذان المصابة بمرض السكر التي تم علاجها بالمستخلصات الإيثانولية المختلفة تحسن في جميع المؤشرات السابقة المقاسة وأفضل تحسن للمجموعة المعالجة بالمستخلص الإيثانولي لنبات الأملج تركيز 400مجم لكل كجم من وزن الجسم.

الكلمات المفتاحية: *الحنظل، الأملج، سكر الدم والأنسولين*