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Pharmacological Study

# Experimental study on effect of hydroalcoholic extract of *Emblica officinalis* fruits on glucose homeostasis and metabolic parameters

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## Abstract

Polyphenols from natural source are potential therapeutics that act alone or supplement anti-diabetic drugs in the prevention and treatment of diabetes. The present investigation was undertaken to study the effect of hydroalcoholic extract (HE) of fruits of *Emblica officinalis* on type I diabetic rats. Diabetes was induced by streptozotocin (STZ) (45 mg/kg i.v.). HE (100 mg/kg, p.o.) was administered for 4 weeks and at the end of treatment, blood samples were collected and analyzed for various biochemical parameters. STZ produced a diabetic state exhibiting all the cardinal symptoms such as loss of body weight, polydipsia, polyuria, glucosuria, polyphagia, hypoinsulinemia, and hyperglycemia associated with hypercholesterolemia and hypertriglyceridemia. Treatment with HE prevented cardinal symptoms and caused significant decrease in fasting serum glucose, $AUC_{glucose}$, cholesterol, triglyceride, low-density lipoprotein (LDL) and very LDL in diabetic rats. However, insulin, $AUC_{insulin}$, and serum high-density lipoprotein level were not significantly altered by treatment. Treatment also reduced lipid peroxidation and increased anti-oxidant parameters in the liver homogenates of diabetic rats. Polyphenol enriched fraction of HE significantly improved disarranged carbohydrate and lipid metabolism of chemically induced diabetes in rats. The mechanism of its anti-diabetic activity appears to be either improvement in peripheral glucose utilization, increased insulin sensitivity, or anti-oxidant property.

**Key words:** Anti-diabetic, anti-hyperlipidemic, anti-oxidant, *Emblica officinalis*, oxidative stress, polyphenol, streptozotocin

## Introduction

Diabetes mellitus is a serious complex chronic condition that is a major source of ill health worldwide. Fruits of *Emblica officinalis* Gaertn. (family Euphorbiaceae) commonly known as "*Amla*" or the Indian gooseberry, have been reported to contain constituents with variable biological activities such as anti-oxidant, adaptogenic, hepatoprotective, anti-tumor, anti-atherosclerosis, immunomodulatory, gastroprotective, hypolipidemic, cyto-protective, and immunomodulating activities.[1] The fruits of *E. officinalis* are used in many medicinal preparations of Ayurvedic and Unani systems of medicine.[2] According to the two main classic texts on Ayurveda, Charaka Samhita and Sushrut Samhita, *E. officinalis* is regarded as "the best among rejuvenative herbs." Since ages *E. officinalis* has been used by practitioners of Ayurvedic system for the treatment of diabetes mellitus in India. Phytochemical investigations of fruits of *E. officinalis* show that it is having high amount of polyphenol content like low and high molecular weight tannins such as gallic acid, 1-o-galloyl-β-D-glucose, esters of gallic acid, methyl gallate, corilagin, furosin, geraniin, emblicanins A and B, punigluconin, pedunculagin, ellagic acid, and flavonoids such as quercetin in the natural form.[3-5] Polyphenols such as tannic acid and flavonoids present in number of medicinal plants are reported to have glucose-lowering,[6,7] lipid-lowering activities,[8-10] and anti-oxidant properties.[11] Therefore, this study was aimed to investigate the possible anti-diabetic and hypolipidemic potential of polyphenol-rich hydroalcoholic extract (HE) of *E. officinalis* fruit and its relation with anti-oxidant activity.

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## Materials and Methods

### Materials

The fresh fruits of *E. officinalis* purchased from Gaziabad (Madhya Pradesh, India) were authenticated by Department of Pharmacognosy. HE of fruits was prepared in pharmaceutical laboratory. Streptozotocin (STZ) was purchased from Sigma Chemicals (St. Louis, USA). Glucose, triglyceride, total cholesterol, and cholesterol high-density lipoprotein (HDL) kits were purchased from Span Diagnostics, Baroda, India. Radioimmunoassay kit for rat insulin was obtained from Bhabha Atomic Research Centre, Mumbai, India. Other chemicals used were of analytical reagent grade.

### Hydro alcoholic extract preparation

Five hundred grams of the powder of dried fruits of *E. Officinalis* were extracted exhaustively with water and methanol mixture at 40-60°C in proportion of 1:1 for 48 h. The HEs thus obtained were filtered and solvent removed under vacuum.

### Phytochemical investigation

#### *Determination of total polyphenols*

HE (100 µl) was mixed with 0.2 ml Folin–Ciocalteu reagent, 2 ml of distilled water and 1 ml of 15% $Na_2CO_3$ solution was measured at 765 nm after being kept for 2 h at room temperature. The total polyphenolic content was expressed as milligrams of gallic acid equivalents/1 g extract.[12]

### Experimental animals

Male Wistar rats weighing 200-250 g were obtained from the animal facility of Zydus Research Centre, Ahmedabad, India. They were maintained under standard environmental conditions (12 h light/dark cycle at 20-25°C and controlled humidity) and provided with feed and purified water *ad libitum*. All experiments and protocols (Protocol No: 06/2005) described in this study were approved by Institutions Animal Ethics Committee and are in accordance with guidelines as per "Guide for the care and use of laboratory animal" and with permission from committee for the purpose of control and suppression of experiments on animals.

### Experimental protocol

Diabetes was induced by single intravenous injection of STZ (45 mg/kg) dissolved in freshly prepared 0.1M citrate buffer (pH = 4.5).[13] To prevent the hypoglycemia that occurred during the first 24 h following the STZ administration, 5% glucose solution was orally given to the diabetic rats. After 48 h of STZ injection, animals showing glucosuria (>2%) were divided into two groups of six rats each: Diabetic control and diabetic treated with HE (100 mg/kg/p.o./day). Further, two more groups one treated with vehicle and another treated with HE (100 mg/kg/po/day) were also included in the study for comparison with diabetes-induced groups. Treatment was started after 3 days of STZ injection and it was given daily for 4 weeks. Daily food, water intake, and body weight gain were measured.

### Blood sampling and biochemical analysis

At the end of 4-week treatment, the animals were kept for an overnight fasting and the blood samples were collected from retro-orbital plexus and allowed to clot for 30 min at room temperature. These blood samples were centrifuged at 5000 rpm for 20 min and serum was separated and stored at –20°C until analysis was done. Serum samples were analyzed spectrometrically for serum glucose, triglyceride, total cholesterol, and HDL cholesterol, using their respective kits and an UV-visible spectrophotometer (Shimadzu UV-1601, Japan). Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were calculated from the values of total cholesterol, triglyceride, and HDL. Serum insulin was estimated by a radioimmunoassay technique using the gamma counter (Packard).

The same animals were subjected to Oral glucose tolerance test on next day.[14] To perform OGTT, the animals were orally administered with 1.5 g/kg of glucose and blood samples were collected from the tail vein under light ether anesthesia before, i.e. 0 min and 30, 60, and 120 min after oral glucose administration. Samples were analyzed spectrometrically for serum glucose, and serum insulin was estimated by a radioimmunoassay technique using the gamma counter. Plotting the glucose concentration versus time gives a curve showing rise and fall in glucose and insulin levels with time and expressed as integrated area under the curve for glucose and insulin ($AUC_{glucose}$ and $AUC_{insulin}$).

### Assessment of oxidative stress-related markers

Liver tissues were finely sliced and homogenized at 12000 × g in chilled Tris-buffer (pH 7.4). The homogenate was centrifuged and a clear supernatant was used for estimation of various anti-oxidant parameters such as superoxide dismutase (SOD), catalase, lipid peroxidation or malondialdehyde (MDA), and reduced glutathione (GSH). SOD was determined by the method of Mishra and Fridovich,[15] catalase was determined by the method of Aebi,[16] and GSH was determined by the method of Moron *et al.*[17] MDA formation was determined by the method of Slater and Sawyer.[18] The result of anti-oxidant activity in liver was expressed in terms of protein content which was measured as per the method of Lowry *et al.*[19]

### Statistical analysis

Values are expressed as mean ± SEM. The results were analyzed using one-way factorial analysis of variance (ANOVA) followed by Tukey's multiple comparison test using Graphpad Prism 5 software (GraphPad Software, Inc.). The value of $P$ less than 5% ($P < 0.05$) was considered statistically significant.

## Results

### Effects of hydroalcoholic extract on general features and biochemical parameters

Intravenous injection of STZ produced cardinal signs of type 1 diabetes i.e. loss of body weight, polyphagia, and polydipsia in rats. Chronic treatment with HE significantly ($P < 0.05$) prevented loss of body weight, polydypsia, and polyphagia in STZ-diabetic rats. There was no significant effect on the food and water intake of non-diabetic rats [Table 1]. STZ-induced diabetic rats were found to exhibit significant hyperglycemia as compared to control rats. Treatment with HE produced significant ($P < 0.05$) decrease in elevated serum glucose levels. Decrease in serum insulin levels in diabetic rats was increased by the treatment with HE but it is not statistically significant.

It did not produce any significant effect on the serum glucose and insulin levels in non-diabetic rats [Table 2]. STZ-induced diabetic rats were found to have significantly ($P < 0.05$) elevated serum triglyceride, total cholesterol, LDL cholesterol, and VLDL cholesterol levels as compared to non-diabetic control. HDL cholesterol was found to be significantly decreased in diabetic rats. Treatment with HE produced a significant reduction in elevated serum triglyceride, total cholesterol, LDL cholesterol, and VLDL cholesterol levels in diabetic rats. There was an increase in HDL cholesterol; however, it was not statistically significant ($P < 0.05$). Treatment of non-diabetic rats with HE did not produce any significant effects on lipid profile [Figure 1].

### Oral glucose tolerance test

Results of oral glucose tolerance test revealed that $AUC_{glucose}$ is significantly increased in diabetic control as compared to non-diabetic control. Treatment with HE significantly decreased elevated $AUC_{glucose}$ of diabetic animals. $AUC_{insulin}$ of diabetic control was significantly decreased as compared to non-diabetic control group. Treatment with HE did not produce any significant change but produced a slight increase in $AUC_{insulin}$ of diabetic rats as compared to that of diabetic control [Table 2].

### Effects of anti-oxidant parameters in liver

STZ-induced diabetic rats were found to have decreased SOD, GSH, and catalase enzyme levels in liver as compared to control. Treatment with HE produced significant increase in these enzyme levels. Treatment of non-diabetic rats with HE did not produce any effect on the SOD levels as compared to control. While there was slight increase in catalase, GSH level was observed to remain unaltered with treatment of HE in non-diabetic rats [Figure 2]. STZ-diabetic rats were found to exhibit significant increase MDA levels in liver as compared to control rats. Treatment with HE produced significant decrease in MDA levels. Treatment of non-diabetic rats with HE did not produce any significant effect on the MDA levels [Figure 2].

## Discussion

Diabetic rats are reported to have loss of body weight, increased food and water intake which could be due to excessive break-down of tissue proteins and dehydration and catabolism of fats and proteins.[20] Chronic treatment with HE of *E. officinalis* to diabetic rat decreased food and water consumption and prevented loss of body weight and this could be due to decrease in catabolic reaction and a better control of the hyperglycemic state in the diabetic rats. The HE of *E. officinalis* produced decrease in blood glucose levels which indicates that HE possesses anti-diabetic activity. Medicinal plants such as *Terminalia catappa* fruits, *Helichrysum plicatum* leaves, *Lagerstroemia speciosa* leaves, *Punica granatum* flower, *Pterocarpus marsupium* bark, green tea, *Prunus amygdalus* seeds, and red grapes are rich in polyphenols that are reported to be anti-diabetic in various experimental models.[21-24] Polyphenols reported to produce anti-diabetic activity not only in diabetic animals but also in diabetic patients.[25] Results obtained from

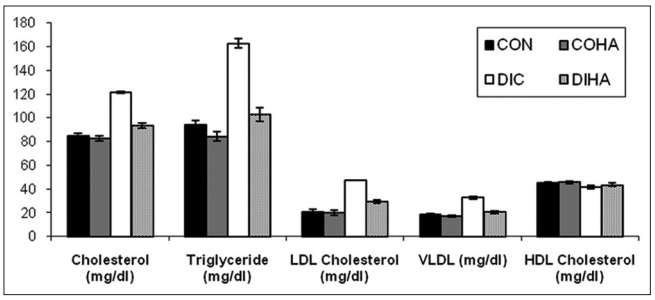


**Figure 1: Effect of chronic treatment with hydroalcoholic extract (HE) of *Emblica officinalis* in non-diabetic control and diabetic rats. Each bar represents mean ± SEM of six animals. CON-non-diabetic control, COHA-non-diabetic control treated with HE, DIC-diabetic control, and DIHA-diabetic animals treated with HE, *: Significantly different from diabetic control animals ($P < 0.05$). (ANOVA followed by Tukey's multiple comparison test)**

**Table 1: Effect of hydroalcoholic extract of *E. officinalis* on general features of non-diabetic control and diabetic rats**

| Parameters | Non-diabetic control | Non-diabetic treated with hydroalcoholic extract | Diabetic control | Diabetic treated with hydroalcoholic extract |
|---|---|---|---|---|
| Body weight (g/100 g animal) | 245.83±6.28 | 245.00±5.03 | 219.23±5.42 | 232.63±5.6* |
| Food intake (g/100 g animal/day) | 30.14±7.12 | 29.31±6.11 | 46.53±0.35 | 35.58±4.82 |
| Water intake (ml/100 g animal/day) | 23.33±6.55 | 24.88±5.44 | 42.08±9.46 | 39.60±8.21 |

Values are expressed as mean+SEM. *Significantly different from diabetic control ($P<0.05$) (ANOVA followed by Tukey's multiple comparison test)

**Table 2: Effect of hydroalcoholic extract of *E. officinalis* on serum glucose and insulin of non-diabetic control and diabetic rats**

| Parameters | Non-diabetic control | Non-diabetic treated with hydroalcoholic extract | Diabetic control | Diabetic treated with hydroalcoholic extract |
|---|---|---|---|---|
| Serum glucose (mg/dl) | 99.09±3.20 | 93.02±4.98 | 392.22±16.52 | 106.22±4.52# |
| $AUC_{glucose}$ (mg/dl min)×$10^3$ | 14.3±0.67 | 11.83±0.64 | 49.56±2.38 | 37.24±2.55# |
| Serum insulin (μU/ml) | 45.90±4.32 | 42.17±4.03 | 23.30±3.66 | 29.17±3.75 |
| $AUC_{insulin}$ (mg/dl min)×$10^3$ | 5.70±0.24 | 5.80±0.42 | 3.28±0.27 | 3.73±0.21 |

Values are expressed as mean±SEM. *Significantly different from diabetic control ($P<0.05$) (ANOVA followed by Tukey's multiple comparison test)

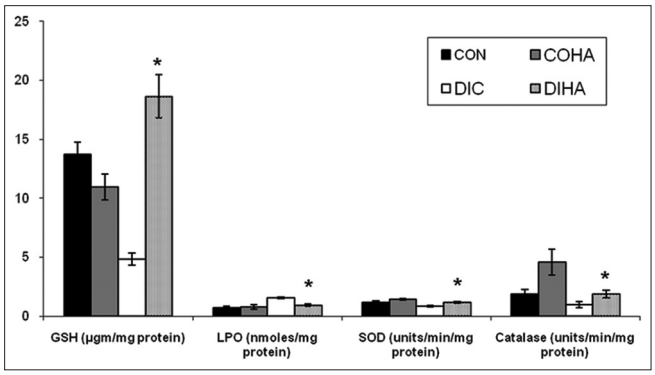


**Figure 2: Effect of chronic treatment with hydroalcoholic extract (HE) of *E. officinalis on anti-oxidant parameters* in non-diabetic control and diabetic rats. Each bar represents mean ± SEM of six animals. CON-non-diabetic control, COHA-non-diabetic control treated with HE, DIC-diabetic control, and DIHA-diabetic animals treated with HE, *: Significantly different from diabetic control animals ($P < 0.05$). (ANOVA followed by Tukey's multiple comparison test)**

phytochemical investigation revealed that the HE possessed higher concentration of total phenols (541.3 mg gallic acid equivalent/1 g extract). A good correlation of anti-diabetic activity and polyphenol concentration in HE of *E. officinalis* was found in our study. Although the HE of *E. officinalis* produced decrease in glucose levels, it failed to improve STZ induced decrease in serum insulin at significant levels. This suggests that the HE possesses anti-diabetic activity which may be due to increased sensitivity of peripheral tissue to insulin or due to a direct insulin-like effect. The result of OGTT also substantiates the findings that HE produced improvement of glucose metabolism in diabetic rat. Concentrations of lipids, such as cholesterol, triglyceride, LDL cholesterol, and VLDL cholesterol were significantly increased in diabetic rats as compared to normal rats which correlate with previous studies in diabetic patients and diabetic rats which could be due to variety of derangements in metabolic and regulatory mechanisms, due to insulin deficiency, which is responsible for the observed accumulation of lipid.[26,27] In this study, chronic treatment with HE of *E. officinalis* exhibited more potent lowering effect on triglyceride, total cholesterol, LDL, and VLDL. These may be due to inhibition of lipolysis in adipose tissue by insulin sensitizing or insulin mimetic effect of polyphenolic fraction of HE of *E. officinalis* because insulin sensitizers and insulin mimetics reported to inhibit lipolysis by inhibiting the activity of the hormone sensitive lipases in adipose tissue. Thus, the results of this study indicate that HE of *E. officinalis* may possess lipid-lowering activity by acting on insulin receptors.

Numerous experimental and clinical observations have indicated that hyperglycemia may directly or indirectly contribute to an increased formation of free radicals. Oxidative stress in diabetes coexists with a reduction in anti-oxidative enzymes such as SOD, GSH, and catalase.[28] A significant decrease in GSH, SOD, and catalase level was observed, which indicates hyperglycemia decreases anti-oxidant capacity due to the accumulation of superoxide anion radicals and hydrogen peroxide. Treatment with HE produced increase in levels of anti-oxidant enzymes; this may result in reduction of hydrogen peroxides and protect the tissues from highly reactive hydroxyl radicals. Study also showed that the increased level of MDA, a marker of fatty chain peroxidation, was significantly increased in diabetes. The treatment with HE of *E. officinalis* decreased MDA level significantly in diabetic rats. Many plant extracts and plant products have been shown to possess anti-diabetic activity having significant anti-oxidant activity.[29] Since *E. officinalis* contains a large amount of polyphenols, it is found to possess significant anti-oxidant activity. Therefore, the presence of polyphenols may be responsible for the anti-diabetic activity of *E. officinalis*.

These findings suggest that there can be a correlation between the higher concentration of total polyphenol contents and anti-diabetic, anti-hyperlipidemic, and anti-oxidant activities. Several anti-diabetic and anti-obesity small molecule from natural source with direct or indirect insulin releasing effect on islet cell, direct insulin-like and insulin mimetic effect have been reported.[30,31] Most of these compounds bind or activate the insulin receptors and have hypoglycemic and hypolipidemic effects in animals.[32] The anti-diabetic activity of polyphenols of *E. officinalis* appears to be mediated through peripheral utilization of glucose either by direct insulin-like or insulin mimetic effect in diabetic conditions. We believe that polyphenols may provide the molecular basis for a new generation of orally deliverable, anti-diabetic molecule with anti-oxidant and anti-hyperlipidemic activities. It distinguishes itself from other drugs by the fact that it not only stimulates glucose transport but also decreases lipid level in diabetes. It is possible that, unlike most other anti-diabetic drugs, HEs of *E. officinalis* may reduce blood glucose without increasing adiposity.

However, many questions remain to be answered. Polyphenols are still a mixture of hydrolysable tannins and flavonoids. What is the most effective compound in these activities? How polyphenols does produce anti-diabetic activity and mediates the inhibition of cholesterol and triglyceride synthesis? Is polyphenols bioavailable *in vivo*? Further investigations are required to be carrying out for structural and functional studies.

## Conclusion

Polyphenol-rich HE of *E. officinalis* ameliorate hyperglycemia, hyperlipidemia, and oxidative stress in animal model of diabetes mellitus. Thus, it can be suggested that the combination of anti-diabetic, anti-hyperlipidemic, and anti-oxidant activities of various polyphenols makes it ideally suited for development of novel phytochemical for the treatment of diabetes mellitus.

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# हिन्दी सारांश

## आमलकी के हाइड्रो अल्कोहोलिक एक्सट्रेक्ट का रक्त शर्करा पर प्रभाव

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इस अनुसन्धान का उद्देश्य आमलकी के पॉलिफिनोलिक हाइड्रो अल्कोहोलिक एक्सट्रेक्ट के सेवन का मधुमेह नियंत्रण प्रभाव को जानना है । चूहे में मधुमेह उत्पन्न करने के लिए स्ट्रेप्टोझोटोसिन (४५ मिली ग्राम/किलो ग्राम) अन्तःशिरा इंजेक्शन दिया गया । आमलकी का एक्सट्रेक्ट (१०० मिली/किलोग्राम) चार सप्ताह तक दिया गया और अन्त में रक्त परीक्षण किया गया तथा विभिन्न बायो–केमिकल पेरामिटर्स की जाँच की गई । स्ट्रेप्टोझोटोसिन से मधुमेह के सभी आधारभूत लक्षण उत्पन्न हुए, जैसे की शरीर भार कम होना, ज्यादा प्यास लगना, मूत्र में शर्करा आना, बार–बार मूत्रप्रवृत्ति, रक्त शर्करा बढना, रक्त ट्राइग्लिसराइड बढना, रक्त कोलेस्ट्रोल बढना, रक्त इंसूलिन कम होना इत्यादि । एक्सट्रेक्ट उपचार के कारण मधुमेह के सभी लक्षण कम होते है एवं ग्लूकोज टोलरेंस टेस्ट में ग्लूकोज स्तर में भी सुधार हुआ है । परन्तु इन्सूलीन स्तर में ज्यादा बदलाव नही आया है । एक्सट्रेक्ट के सेवन से पेरोक्सीडेशन और एन्टि–ऑक्सिडेंट पैरामिटर्स में भी सुधार हुआ है । आमलकी के पॉलिफिनोलिक हाइड्रो अल्कोहोलिक एक्सट्रेक्ट से मधुमेह के कारण ग्लूकोज और लिपिड चयापचय अव्यवस्था में सुधार देखने को मिला है । मधूमेह मे लाभ का कारण या तो ग्लूकोज का बढना, इन्सूलिन सेन्सिटीविटी बढना या एन्टीऑक्सिडेंट अवरोध हो सकता है ।