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The Effect of Aqueous and Hydro-Alcoholic Extract of *Prosopis Farcta* on the Glucose Uptake in L6 Muscle Cell Lines

Rezaei Ensieh, Nazari Najmeh, Nowrouzi Azin, Pakdel Abas, Nazari Hossein*

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Abstract

Introduction: Diabetes is a metabolic disease with high prevalence in all over the world. Treatment with synthetic drugs are just to control it and not effective for an absolute cure, thus, they might not be used by the patients at all. By emphasis on traditional medicine and considering the antioxidant property of medicinal plant, Prosopis *farcta* containing the phenol and flavonoid components, the aim of this study is to evaluate the effect of Prosopis *farcta* extract on the glucose uptake level in L6 muscle cells line. **Materials & Methods:** This is an experimental study in which the cells were grown with DMEM medium in appropriate condition. Cells groups treated with and without glucose uptake stimulation, insulin and aqueous and hydroalcoholic extract of Prosopis *farcta* as well as group by preventing glucose uptake stimulation, Cytochalacin D. To measure the amount of glucose uptake by cells, the instruction of glucose uptake kit (abcam) was used and amount of uptakes was analyzed according to standards. **Results:** Doses of 160 µg/ml of hydro alcoholic extract and 800 µg/ml of the aqueous extract of Prosopis *farcta* have the maximum amount of 2- de- oxy glucose uptake in L6 muscle cells ($p<0/001$) which the dose of 800 µg/ml had the most amount of 2-deoxyglucose uptake in muscle cells ($p<0/001$). The level of differentiation in L6 muscle cells after FBS reduction is more in comparison with FBS 10% and showing that the muscle cells have better biological activity such as 2-deoxy glucose uptake. **Conclusion:** Findings showed that both aqueous and hydro alcoholic extract of Prosopis *farcta* have been effective in reducing the added 2-deoxy glucose of medium and increased the level of glucose uptake. This effect promoted by increasing the extract dose which is concentration dependent manner. However, it is necessary that the accurate role of this plant would be investigated in molecular surveys.

Keywords: *Prosopis farcta*, glucose uptake, L6 muscle cells, Insulin

Introduction

Diabetes is a metabolic disease in most of the developed and developing countries and is appeared in the form of chronic disorder in the metabolism of carbohydrates, proteins and fats. These problems are due to relative or absolute insulin deficiency or insulin resistance (Arumugam, Manjula and Paari, 2013). This metabolic disorder leads to increase the blood sugar and in the long-term causes damages to tissues and organs, and if it not diagnosed early or lack of continuous control, the life is threatened, however, World Health Organization (WHO) estimates that approximately, 3 million people are dead due to diabetes (George, Lochner and Huisamen, 2011). Today, 5% of the world's population are suffering from diabetes mellitus and within the next 25 years, it will be one of the main causes of fatal and debilitating factors for human beings (Jarald, Joshi and Jain, 2008). According to recent international diabetes federation (IDF) survey, almost 170 million people (2010) around the world were suffering from this disease. And it is predicted that this figure will be reached to double. However, it is half of the real cases, because half of people with diabetes have not been diagnosed and detected. Indicating impressive incidence of the disease in communities. The rapid growth can be due to various reasons including obesity, unhealthy diet and inactivity. Thus, drug treatments and lifestyle changes are prescribed and recommended (Prabhakar and Doble, 2011).

The up taken glucose in the blood in normal case causes the rapid secretion of the insulin. This hormone is necessary for glucose entry into the cells through the cell membrane by the glucose-mediated transport proteins. The shortage of insulin or any resistance to this

Rezaei Ensieh
Department of Biochemistry, Semnan University of Medical Sciences, Semnan, Iran
Student research committee, Semnan University of Medical Sciences, Semnan, Iran.

Pakdel Abas, Nazari Hossein*
Department of Biochemistry, Semnan University of Medical Sciences, Semnan, Iran.

Nazari Najmeh
Department of Biochemistry, Faculty of basic Science, Azad University, Science and Research branch, Tehran, Iran.

Nowrouzi Azin
Department of Biochemistry, Tehran University of Medical Sciences, Tehran, Iran.

***Email:** hosnazbio@yahoo.con

hormone in body causes a significant imbalance in the uptake of glucose and leads to increase the fasting glucose and postprandial glucose (Prabhakar and Doble, 2011; Saltiel and Kahn, 2001; Qi et al., 2010). The message of insulin goes ahead the intracellular metabolic machinery in order to create the desired effects. A few seconds after insulin binding to the membrane receptors, about 80% of the cell membranes, especially the muscle and fat cells are highly permeable to glucose. There are various molecules of protein transferring the glucose that are bound to the cell membrane and facilitate the glucose uptake into the cells which the most important transporter is GLUT4 as well (De Vos et al., 1995; Perriott et al., 2010; Hall ACGaJE, 2006). Hyperglycemia, hyper/ hypo lipidemia and hyper- aminoacidemia which occur due to reducing insulin secretion or decreasing the insulin function are the indicators of diabetes. Due to these changes, diabetes is accompanied with the progressive trend of complications; the hyperglycemia plays the important role in progressing the complications (Rao et al., 2010; Fowler, 2008; Association, 2006; Modak et al., 2007; Said et al., 2008). Unfortunately, despite the great steps taken in treating and managing the diabetes, we are witnessing a constant upward trend in diabetes complications and mortality rate (Tiwari and Rao, 2002). But due to the restrictions on synthetic drugs, medical science is searching for the options with fewer side effects and high efficiency. Plants due to their effects on diseases, fewer side effects and reasonable prices have been used as the natural resources in the world for a long time. In ancient texts, more than 800 plants with anti-diabetic effects have been reported and investigation in pharmacology of ethnics indicates that there are more than 1200 plants known to reduce the blood sugar levels. The herbal medicines have been used in all cultures as a source to treatment the disease from ancient times. In diabetes, there are alternative drugs which are able to remove the symptoms of diabetes and prevent its complications. Also, there are some drugs which can regenerate the cells of pancreas, relieve the insulin resistance, increase the antioxidant activity and also reduce the cholesterol level. To manage the patients with type- 2 diabetes via medicines which reduces the blood glucose levels and also stores glycogen in liver is possible, while there is no drug among the modern medicine with this property. Today, the hypoglycemic effect in some plants, has been proven in animal model and in human type -2- diabetes model and some of the common drugs have been taken of the effective substance of these plants. Metformin as a bigovanoid with low toxicity and high potential in reducing the blood sugar is produced from a plant. Regardless its dosage, it is the only drug that is prescribed for patients. There are also other herbal medicines that have been successful in treating the diabetes, which is investigates herbal medicines play an important role in treating the diabetes (Jarald, Joshi and Jain, 2008; Prabhakar and Doble, 2011). One of the plants used to control diabetes is Prosopis farcta (scientific name) is known Kahoorak plant (Persian name) and its english name is Syrian mesquite. It is a hypoglycemic drug which is used in traditional medicine to treat the patients with diabetes (Fariba et al., 2013). This plant is from Legumiosea family and the sub-family of Mimosoideae which is a native and grown in arid and semi-arid area in America, Asia and Africa as well as is found in Asia; in the western part of India and from China to Iran and Iraq. P. farcta contains secondary metabolite and effective compounds such as alkaloids; 5 hydroxyl L-arabinose, Lektine, Apignine and tryptamine. Also, the ethanol extract of this plant contains alkaloid, tannin, glycoside, flavonoid and saponin. In Iran and in some countries, this plant is used to treat a range of diseases, for example, the leaves of P. farcta are used in treating the diarrhea, coughs and colds. Recently, the neuro-protective and therapeutic effects on diabetic foot ulcers have been proven as well. In Jordan, the extract of the roots are used to treat diabetes. The other therapeutic effects of this plant are therapeutic effects on stomach ulcers, rheumatism, and laryngitis, angina and dyspnea. In other studies, the anti-spasmodic, the anti-inflammatory and also pain relief properties have been mentioned. As it was mentioned, some of the applications of this plant have been proven in new researches. However, most of this plant usage is rooted in general culture of each region, and these properties have not been proven by scientific authorities (Ranjbar Heidari, Khayyat-Zadeh and Keshtahgar, 2012; Hajinejad et al., 2015).

So In this study surveys the effect of aqueous and hydro-alcoholic extract of P. farcta on the glucose uptake level in L6 muscle cells. L6 muscle cells is a kind of cell line isolated from the primary fibroblastic embryonic cells of the mouse and used in research on fat tissues. (Atanasov et al., 2013; Sonksen and Sonksen, 2000). Since no study has been conducted on the effect of stimulating glucose uptake by the P farcta on cultured cells. Thus, for further investigation and possible confirmation of researches on laboratory animals, we decided to evaluate the effect of aqueous and alcoholic fruit extract of P. farcta on the amount of glucose uptake in the L6 muscle cells line.

Methods and Materials:

Materials and necessary tools which were used in this study are as follow: DMEM High and Low glucose medium for general growth and to exposure differentiation and the drugs respectively. Cultured plates, insulin, glucose, glucose uptake measurement kit (Abcam #: ab136955, Version 2015), Cytochalacin D, ELISA Reader, inverted microscope (Nikon), and a shaker incubator.

Extract preparation:

Firstly, the fruit of the plant was collected from a region around the Semnan city and was confirmed by the experts at the agricultural Research Center in Semnan province before was dried in a proper condition by considering the light, temperature and humidity of the chamber. To prepare the hydro-alcoholic extract with ethanol / methanol / water solvent (10, 30, 60), Soxhlet extractor as a lab device was used. 50 grams of P. farcta fruit was solved into 500 ml of solvent. Then, they were heated at 30-40 ° C for two hours, and the hydro-alcoholic extract was prepared. Then the rest of water was concentrated by rotary machine and the dried powder was collected and kept in the proper temperature for testing. Also, to prepare the aqueous extract of the fruit of P. farcta, the distiller in water was used. 100 grams of the fruits of P. farcta was dissolved in 1000 ml of distilled water. Then, it was heated at 30 to 40 ° C for two hours, and then extract was filtered. The remaining residue on the filter was dried using the oven completely. Powder of alcoholic and aqueous extracts prepared via the extract process were used at concentrations of 20, 40, 80, 160 and 400 and 800 micrograms per milliliter respectively which were exposed to the cultured cells.

Cell preparation and cell culture:

In this study, L6 muscle cells line which had been purchased from the Pasteur Institute **w**ere used in various groups with culture medium (DMEM) along with 10% FBS and the appropriate antibiotics under the equal and standard condition of the lab. The cultured samples using census method were studied in biochemistry laboratory in Semnan University of Medical Sciences and the amount of up- taken glucose was measured and calculated.

The assessment 2-deoxy-glucose uptake

The effect of extracts on the 2-deoxy-glucose uptake via the cultured cells is tested. The 2 - Deoxy-glucose up taken by cells using the glucose measurement kit instruction was done as follows: The L6 muscle cells culture, 1500 cell/well in 100 µL of FBS 10%, DMEM medium in 96- well plate and the cultured cells were incubated in 37 °C and CO2 5% and differentiated cells obtained after five days by using FBS 2%. The cells were incubated with 100 µl KRPH / 2% BSA for 40 minutes to make a severe glucose starvation after washed with phosphate-buffered solution (PBS). Cells in control group were washed for three times with PBS and were kept until cell lysis step but cells in treated group were exposure to 10 nM insulin for 20 min to activate glucose transporter proteins in cells, 1 µM Cytochalacin D for 30 min (as an actin filament arrangement inhibitor) and the herbal extracts, four treatment groups (glucose uptake stimulation with the hydro alcoholic extract of P. farcta) with the concentrations of 20, 40, 80, 160 µg/ml and two glucose uptake stimulation groups with aqueous extract of P. farcta with concentrations of 400 and 800 µg/ml for 30 min. 10 µL of 10mM (2-Deoxy Glucose, 2-DG) solution is added to cells and were incubated for 20 min after mixing. Then 80µL Extraction buffer add to each well for down lysis of cells and the cell lysed solution is heated at a temperature of 85 ° C for 40 minutes that the intracellular NADPs are removed from cells and the enzymes existing in the sample will be destroyed. Then freeze the cell lysates on ice for 5 minutes and neutralize them with 10 µL neutralization buffer before transfer supernatant to new tubes**.** Reaction is conducted in a flat bottom -96- well micro plate and it is recommended to dilute samples 1/10 in assay buffer to a total volume of 50 µL. According to the kit instructions; 10 µ L of Reaction Mix A. (NADPH generation) is added to each well and incubated for one hour at 37 ° C . Then 90 µ L of extraction Buffer is added to each well and micro plate is sealed by para film and is heated for 40 minutes at 85°C to degrade any NADP left in the sample. Microplate is incubated on ice for 5 minutes to be cooled and the reaction is neutralized by adding 12 µL of neutralizing buffer. Then according to the instructions kit 38 µ L of Reaction Mix B is added to each well and, they are mixed well by pipetting. Absorbing the color complex which has been produced in the wells with wavelength of 412 nm is recorded using the ELISA micro plate reader. Then, received data are analyzed on the basis of the kit instructions.

Data analysis:

Data were recorded and analyzed via SPSS-23. To describe Numerical variables statically, mean and standard deviation (mean±std. deviation) are used. And for categorical variables, number and percentage (count & percentage) are reported. Data were analyzed via- Chi- Square-2 Test or Fisher's Test and T-test or equivalent to its nonparametric (U-Mann-Whitney) and Pearson correlation coefficient. In all tests, the reliable level was considered 95% and the significant level was less than 0.05.

Results

Differentiation in L6 muscle cells plays an important role in biological function which about 5 day later after FBS reduction; the differentiated cells were tested for 2-deoxy glucose uptake.

A. The effect of P. Farcta fruit hydro alcoholic extract on glucose uptake in L6 muscle cells

L6 muscle cells were exposed to P. Farcta fruit hydro alcoholic extract at doses of 20, 40, 80 and 160 µg/ml along with Cytochalacin D "as actin filaments depolymerization agent" and the glucose uptake in L6 muscle cells was evaluated. Insulin stimulated glucose up take increased significantly in comparison with control group which is shown in figure 1 which has been reduced with cytocalasin D. Data analysis using Chi-square test showed that by increasing the concentration of P. Farcta fruit hydro alcoholic extract glucose uptake in L6 muscle cells line had increased significantly ($p>0.001$); So that according to Figure 2, glucose uptake level in L6 muscle cells at the doses 80 and 160 µg/ml of P. Farcta fruit hydro alcoholic extract was maximum and with Cytochalacin D an actin filaments polymerization inhibitors decreased significantly ($p<0.001$).

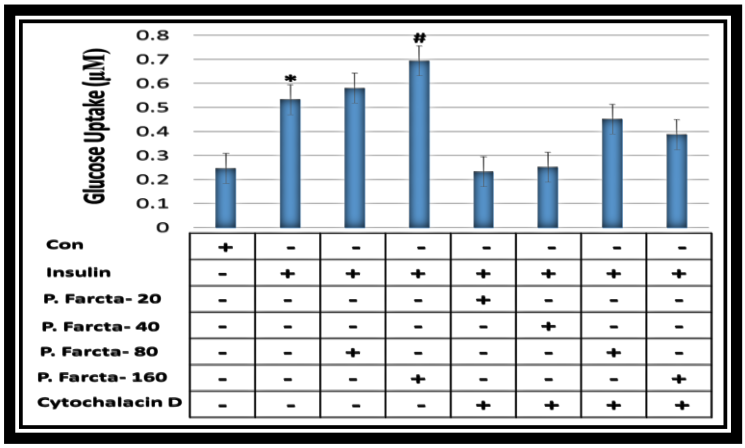

Figure 1: P. farcta fruit hydro alcoholic extract at the doses 20, 40, 80 and 160 µg/ml with Cytichalacin D (actin filaments polymerization inhibitor) on glucose uptake in the L6 muscle cells. * P≤0.001, # P≤0.001.

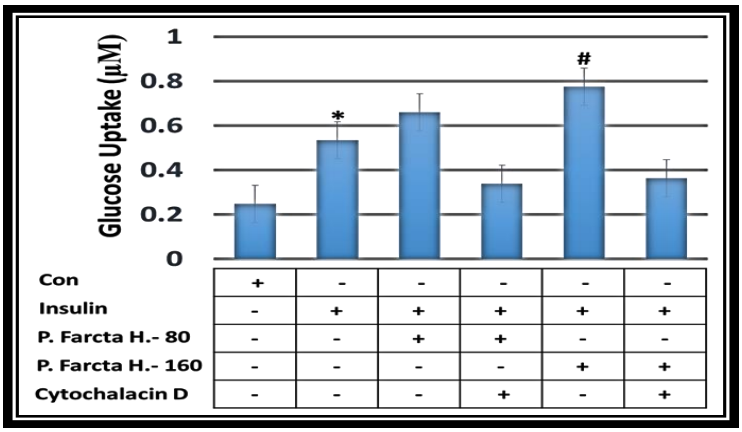

Figure 2. The effect of Cytochalacin- D on glucose uptake level with insulin and hydro alcoholic P. farcta fruit extract in L6 muscle cells. * P≤0.001, # P≤0.001

B. The effect of P. Farcta aqueous extract on Glucose uptake in L6 muscle cells

Fruit aqueous extract of P. farcta at the doses of 400 and 800 µg/ml were exposed with L6 muscle cells and glucose uptake was investigated. The results have been shown in figures 3, according to this figure, 2-deoxy-glucose uptake with 10 nM insulin have increased significantly. Data analysis using Chi-square test showed that by increasing the concentration both in aqueous and in hydro alcoholic extract of P. farcta with a significant correlation, the percentage of glucose uptake in L6 muscle cells line had increased (p>0.001); and according to figure 4, the doses of 160 µg/ml of alcoholic extract and 800 µg/ml of the aqueous extract of P. farcta have the highest glucose uptake level in L6 muscle cells. Among the aqueous and alcoholic extract of P. farcta, the dose of 800µg/ml of the aqueous P. farcta fruit extract has more glucose uptake in L6 muscle cells line.

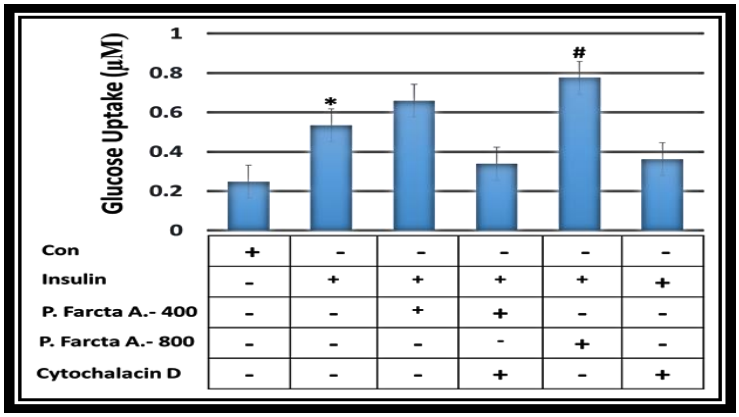

Figure 3, the effect of aqueous P. farcta extract on glucose uptake level with insulin in L6 muscle cells line (P≤0.001, # P≤0.001).

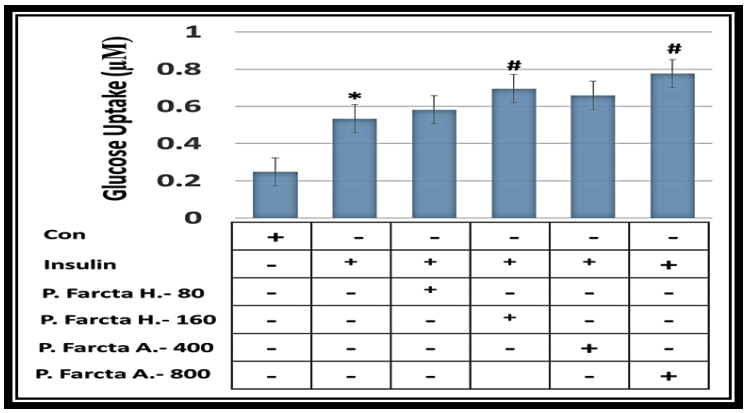

Figure 4: the effect of hydro alcoholic P. farcta fruit extract at doses of 80 and 160 and the aqueous P. farcta fruit extract at doses of 400 and 800 µg/ml on glucose uptake level in L6 muscle cells line (* P≤0.001, # P≤0.001).

Comparisons effect of hydro alcoholic P. Farcta fruit extract at doses of 20, 40, 80 and 160 and aqueous P. farcta fruit extract at doses 400 and 800 µg/ml on glucose uptake level in L6 muscle cells with Cytochalacin D are shown in 5. The results have been shown that in presence of any stimulator "as a control group" the cells have no reaction but in the presence of insulin there is significantly increased glucose uptake. Data analyze by T -Test shows glucose uptake level in L6 muscle cells line in hydroalchoholic and aqueous extract at doses of 160 and 800 µg/ml are more than lower dose treated cells ($p<0.001$). So, aqueous or alcoholic P. farcta fruit extract stimulated glucose uptake has been increased significantly in L6 muscle cells by concentration dependent manner which is a significant lower glucose uptake with cytocalasin D. ($P<0.001$) (Figure 5).

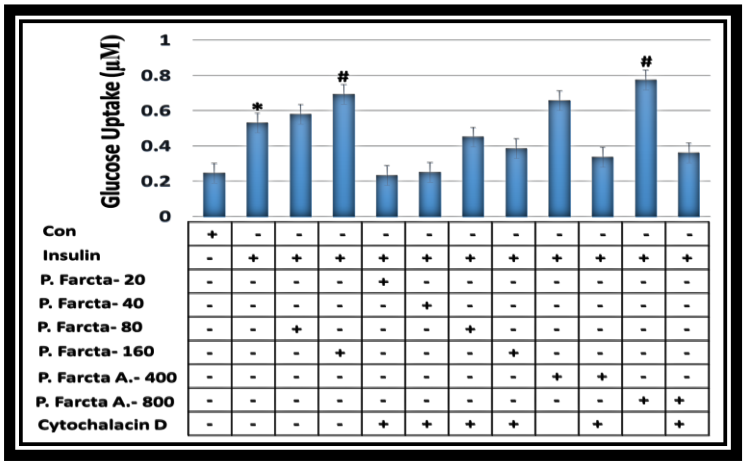

Figure 5: the comparisons of hydro alcoholic P farcta extract at doses of 20, 40, 80 and 160 µg/ml and aqueous P. farcta extract with doses of 400 and 800 µg/ml on glucose uptake in L6 muscle cells with Cytochalasin-D (actin filaments polymerization inhibitor), * P≤0.001, # P≤0.001.

Discussion and conclusion:

Dramatic increase in the metabolic syndromes, obesity, insulin resistance and lipid disorders have caused diabetes mellitus as a metabolic disorder has been epidemic and has a preat share among metabolic disorders. Today, there are some drug categories to decrease blood sugar in medical world; including sulfonylureaes, Meglitinids, Bigoanids and Alfa-glucosidases inhibitors. A prospective study on diabetes in UK has shown that keeping the normal levels of blood sugar can prevent the vast majority of diabetes consequences. Unfortunately, the current drug regimens are not able to establish a sufficient regulation of blood sugar in diabetic patients (Chakrabarti and Rajagopalan, 2002). Herbal medicines are not only outdated but also play an important role in human health care (Chang et al., 2013).

So this study examines one of variant herbal medicines called P. farcta. to treat diabetes and according to the extensive researches, this study is the first study which is evaluating the effect of aqueous and alcoholic P. farcta fruit extract on glucose uptake in L6 muscle cells using cell culture method. In this study data analyze that is based on 2-deoxy glucose uptake amount which enter the cells shows that after exposing cells with alcoholic and aqueous P. farcta fruit extract there is a significant change in such a way that by increasing the concentration both in the alcoholic and in the aqueous extract of P. farcta fruit, the glucose uptake level in L6 muscle cells is increased, so that the doses of 160 µg/ml of alcoholic extract and 800 µg/ml of the aqueous extract have the most amounts of glucose uptake in L6 muscle cells. Among the aqueous and alcoholic of P. farcta fruit extracts, dose of 800 µg/ml of aqueous P. farcta fruit extract has more amount of glucose uptake in L6 muscle cells. So, we can say that glucose uptake level in L6 muscle cells with doses of 160 µg/ml of

hydro alcoholic extract and 800 µg/ml of aqueous extract have been more (significantly) than the treated cells with the lower doses which by increasing the concentration both in the alcoholic extracts or in the aqueous extract of P. farcta fruit, the percentage of glucose uptake has been increased significantly in L6 muscle cells.

The other studies with different methods have been conducted to assess the effect of this plant on diabetes. In a study was carried out (2016) by M. Dashtban et al., shown that the blood glucose level in the streptozotocin-induced diabetic rats had significantly been reduced after exposing with the P. farcta fruit extract (Dashtban, Sarir and Omidi, 2016). Also, in a study (2008) conducted by Edwin Jarald entitled "Diabetes and herbal medicines"; is suggested that the P. farcta is one of the several plants used in treating the diabetes in Jordan and parts of Asia, as well as in some other places in the world and is used as an anti-diabetes drug (Jarald, Joshi and Jain, 2008). On the other hand the results of a screening study (2014) conducted by Emad et al. indicate that aqueous extract of P. farcta has no significant role in decreasing the plasma glucose of the Alloxan-induced diabetic rats and rabbits. In this study the researchers did not clearly determine the formulation of extract and the extracted organ in this study. Sometimes, the whole plant extract has no significant effect on treatment of certain factor, while the extract of different parts of plant can be effective in the treatment of disease (Twaij and Al-Dujaili, 2014).

The study (2013) that is done by M. Minaian et al shows that root extract of this plant was not effective in lowering blood sugar. According to the type of P. farcta organ to reduce blood sugar and contradictory studies, it seems that the P. farcta fruit plays an important role to reduce blood sugar level (Fariba et al., 2013). Beside the anti-diabetic property of P. farcta, it has some other properties such as wound healing effect in diabetic ulcers so that wound healing is in trouble cause of high blood sugar and its oxidative metabolites and metabolites deposition. The other properties of this plant such as anti-inflammatory, vascularization and epithelialization properties which are effective in the process of diabetic wound healing. To confirm this property are different researches done by Gina Khayat zadeh and Azadeh Ranjbar (2012). They examined the effect of Fruit Pod Powder and aquatic extract of P. farcta on Healing Cutaneous wounds in Diabetic Rats that resulting P. farcta as a plant with lowering blood sugar, vascularization and anti-inflammatory properties is effective in wound healing of streptozocin induced diabetic rats (Ranjbar Heidari and Khayyat-Zadeh J, Keshtahgar, 2012; Ashfaq, 2013; Ranjbar-Heidari et al, 2012).

In various studies, the effect of aqueous and alcoholic extracts of P. farcta on glucose uptake and consequently diabetes treatment due to various properties of this plant have been reported. One of these properties is the anti-diabetic and antioxidant property of this plant in diabetes, there is no balance between body's antioxidant defense system and the production of free radicals and the amount of free radicals increases. These oxidant factors cause lipid peroxidation and Malondialdehyde (MDA) production (Hajinejad et al., 2015).

Present study is one of the first studies to evaluate the effect of aqueous and alcoholic P. farcta fruit extract on glucose uptake in L6 muscle cells using cell culture method. So we can say this study has been able to investigate the therapeutic properties of this plant for diabetes by evaluating the hydro alcoholic and aqueous P. farcta fruit extract on glucose uptake with different doses as a new subject with cell culture method. However, it is suggested that different doses of the other parts of P. farcta in vivo should be evaluated beside of and more accurate inspections on the effective compounds existing in this plant.

Conclusion:

The results of data analyze in this study which is based on 2-deoxy glucose uptake level shows that glucose uptake level after exposing the cells with hydro alcoholic and aqueous P. farcta extract was changed that by increasing the concentration both in the alcoholic and aqueous extract of P. farcta, the glucose uptake level increases significantly in L6 muscle cells ; so that hydroalcoholic extract with 160 µg/ml and aqueous extract with 800 µg/ml have maximum glucose uptake in L6 muscle cells. Between the aqueous and hydroalcoholic P. farcta fruit extract, the dose of 800 µg/ml of aqueous P. farcta extract has the most glucose uptake level in L6 muscle cells. Also, the glucose uptake in doses of 160 µg/ml of hydro alcoholic extract and 800 µg/ml of aqueous P. farcta extract in L6 muscle cells have been more than the treated cells with the lower doses significantly which is by increasing the concentrations both in the alcoholic extract and in the aqueous P. farcta fruit extract, the glucose uptake in L6 muscle cells is increased significantly. Thus, increasing 2-deoxy-glucose uptake in the hydro alcoholic and aqueous extract is dose dependent manner. On the basis of this study's results and further studies regarding P. farcta effective materials and lowering glucose level property of this plant, it is expected by using these properties we would be able to treat the diabetes and to control its complications in human body; in fact it needs to more accurate and clinical studies.

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