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EFFECT OF AQUEOUS EXTRACTS OF (*CITRUS LIMON*) SEED ON SOME PHYSIOLOGICAL AND BIOCHEMICAL PARAMETER IN ALLOXAN INDUCED DIABETIC MALE ALBINO RATS

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ABSTRACT

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia(increase mount of insulin)according to grotesque in insulin secretion, insulin action or both Diabetes milletus is one such disease which is causing serious trouble to human health, In addition to that rapid increase in diabetesmilletus is becoming a serious menacing to mankind in all parts of the world, The result parameters showing that there is a significantly increased ($p< 0.05$) in sugar compared to control in group while there is a significantly increased ($p< 0.05$) in cholesterol, triglyceride, LDL, AST, ALT in diabetic rats compared to control. While show significantly decreased in HDL in diabetic when used extract of *Citrus limon* is decreased the levels of (sugar, cholesterol, triglyceride, AST, ALT) and improve the level of HDL Because have many phytochemical such as (saponin, flavonoids, antioxidants). Also showing significantly decreased ($p< 0.05$) in WBC, RBC, Hb in Diabetes mellitus, but when use ECl that increase the amount of (WBC, RBC, Hb).

KEYWORDS: Diabetes Milletus, ED, Amyral, Citrus Limon Seed, ECL

INTRODUCTION

Diabetes mellitus is chronic metabolic disorders that effect human body in physical, psychological and social health, also defined as a group of disorders characterized by hyperglycemia, change metabolism of lipids, carbohydrates and proteins(Patel *et al*.,2011; Warjeet,2011).It is becoming the third "killer" of the health of mankind along with cancer, cardiovascular and cerebrovascular illnesses(Chauhan*et al*.,2010).

Knowledge about diabetes mellitus found in ancient Egypt and Greece. The word "diabetes" is derived from the Greek word "Diab" (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); "mellitus" is the Latin word for "sweetened with honey" (refers to the presence of sugar in the urine (Warjeet, 2011) . The diabetes Classify of

According to American Diabetes Association (ADA,2014) diabetes can be classified into four clinical categories:

- Type 1 diabetes (due to b-cell destruction, usually leading to absolute insulin deficiency.
- Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance.
- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy thatis not clearly overt diabetes
- Other specific types of diabetes due to other causes, e.g., genetic defects in b-cellfunction, genetic defects in insulin action, diseases of the exocrine pancreas (suchas cystic fibrosis), and drug- or chemical-induced (such as

in the treatment of HIV/AIDS or after organ transplantation(ADA,2014).

- Experimental diabetes (ED) can be induced by pancreatectomy, administration of insulin-antagonist hormones or other chemical agents such as alloxan and streptozotocin. There are three groups of chemical agents used to induce ED, the first group destroys the beta cells of the pancreatic islands; the second group alters the beta cells but do not destroy them and the third group elevate the endogenous insulin requirements weakening the pancreas and producing ED (Akter*et al*.,2014).

Symptoms of Diabetes

The classical symptoms of diabetes are polyuria(frequent urination), polydipsia(increased thirst) and polyphagia(increase hunger), Symptoms may develop rapidly (weeks or months) in type 1DM while in type 2DM they usually develop much more slowly and may be subtle or absent, Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eye, resulting in vision changes (McMillan-Price*et al*.,2006)

Diagnosis of Diabetes

The American Diabetes Association (ADA) issued diagnostic criteria for diabetes mellitus:

- Glycated hemoglobin (HbA1C); the value≥6.5%. The test should be performedin a laboratory using a method that is the National Glycohemoglobin Standardization Program (NGSP) certified and standardized to theDiabetes Control and ComplicationsTrial (DCCT) assay.
- Fasting plasma glucose (FPG); the value≥126 mg/dL (7.0 mmol/L). Fastingis defined as no caloric intake for at least 8 hr.
- Oral glucose tolerance test (OGTT); the value ≥200 mg/dL (11.1 mmol/L)during two-hour. The test should beperformed as described by the WHO, using a glucose load containing three quivalent of 75 g anhydrous glucosedissolved in water.
- Random plasma glucose (RPG); the value≥200 mg/dL(11.1 mmol/L)in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis(ADA,2014).

Diabetic Complications

Diabetes milletus also causes "microvascular" complications leading to the small blood vessels damage, Diabetic retinopathy, affects blood vessel formation in the retina of the eye, can lead to problems in vision like reduction of vision, and potential blindness(Svenssonet *al*.,2004)Diabetic nephropathy, the other complication of diabetes on the kidneys can lead to drastic changes in the kidney tissue, loss of progressively larger amounts of protein in the urine, and gradually leading to chronic kidney disease requiring dialysis, Diabetic neuropathy is the complication of diabetes effecting the nervous system, most commonly causing numbness, and pain in the feet and also increasing the risk of skin damage due to altered sensation(Saely*et al*.,2004).Diabetic neuropathy is a vascular disease effecting circulation of blood in the legs, contributing to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that are difficult to treat and occasionally require amputation .(Amos *et al*.,2010)

Drugs Controlling Diabetes Mellitus and Their Mechanism of Action

The common method for treatment focused mainly on regulating and decreasing

blood sugar to fall within the normal level, The main mechanisms in both traditional and Western medicines involve decrease blood sugar through stimulating pancreatic β-cells and inhibiting other hormones elevating blood sugar, increasing the affinity and sensitivity of insulin receptor and lowering glycogen release also enhancing glucose utilization within many tissues and organs, clearing free radicals, resisting lipid peroxidation, correction of the lipid and protein metabolic disorders and improving human blood circulation. (Singab *et al*.,2014).

The present oral antidiabetic sulfonylureas that decrease blood sugar mainly by elevating insulin release from islets of Langerhans, They combine with sulfonylurea receptor on β-cells resulting in adenosine triphosphate–dependent potassium channels closure. biguanides they reduce hepatic gluconeogenesis and replenish peripheral tissues' sensitivity to insulin through elevating insulin-stimulated uptake and utilization of sugar, biguanides are ineffective in insulin absence, The best example of this classis metformin. The alpha-glucosidase inhibitors "starch blockers" inhibit certain enzymes responsible for the breakdown of carbohydrates in the small intestine. They act mainly by decreasing the rate of carbohydrate absorption in the body. acarbose, an importantexample in this class. Thiazolidinediones (TZDs). Their primary mechanism of action includes improving of muscle and adipose tissue sensitivity to insulin and to a smaller extent; reducing liver glucose production. TZDs are potent and selective agonists to the nuclear peroxisome proliferatoractivated receptor- gamma present in liver, skeletal muscle and adipose tissue (Singab*et al*.,2014)

Glimepiride is a second-generation SU primarily activating specific receptors (SURs) on pancreatic β-cell membrane. ATP-sensitive potassium channels close, thus resulting in an augmented trans-membrane calcium flux and insulin release from β-cells Among SUs, only glimepiride is internalized in the cell and is able to stimulate both first and second phases of insulin secretion.(Korytkowski *et al*.,2002)

Medicinal Plants

The term of medicinal plants involve a various types of plants used in herbalism and some of these plants have a medicinal activities, These medicinal plants consider as a rich resources of ingredients which can be used in drug development and synthesis

These days the term "Alternative Medicine" became very common in western culture, it focus on the idea of using the plants for medicinal purpose, But the current belief that medicines which come in capsules or pills are the only medicines that we can trust and use, Even so most of these pills and capsules we take and use during our daily life came from plants. Medicinal plants frequently used as raw materials for extraction of active ingredients which used in the synthesis of different drugs(Hassan,2012) .this study include: seed *of Limon citrus* and effect on diabetes, Lemon is an important medicinal plant of the family Rutaceae, The tree reaches 3-6m in height and usually has sharp thorns on the twigs, The alternate leaves, reddish when young, become dark-green above, light-greenbelow are oblong, The fruit is oval with anipple-like protuberance at the apex (7 -12 cm) long, the peel is usually light-yellow though some lemons are varie gated with longitudinal stripes of green and yellow or white, lemon is primarily important for its vitamin C & potassium content, it is aromatic,dotted with oil glands, Some fruits are seedless but mosthave a few seeds (Laszlo,2007)

·Seeds of lemon are pale whitish to greenish, flattened, and angular; the seeds are usually polyembryonic, meaning they have multiple embryos that can germinate, Theembryos are either zygotic or nucellar, the zygotic embryos are derived from pollination of the ovary and therefore are not always similar in horticultural qualities to the parent tree, the nucellar embryos are derived wholly from the mother plant and display very similar characteristics to the parent plant(Dugo& Digiacomo,2002).

Medicinal Uses

Lemon act as antioxidant The mechanisms of antioxidant action can include inhibition of reactive oxygen species formation by suppressing enzymes involved in free radical production; scavenging reactive oxygen species; and protecting antioxidant defenses (Liu *et al.*,2012)Anticancer such as flavonoids and limonoids Limonoids constitute one of the major phytochemicals along with flavonoids, coumarins, and carotenoids in citrus. Limonoids were shown to possess cancer preventive properties (Miller et al., 2004). hot water extract of lemon seed have antimicrobial activity against bacterial (Staphylococcus aureus, Pseudomonas aeruginosaand Escherichia coli) and fungal (Candida albicans, Microsporumcanis, Trichophytonrubrum and Aspergillusniger) pathogens are documented (Pandey et al.,2011).Antidiabetic activity Flavonoids found in Citrus limon includes hesperidin, quercitrin, eriocitrin, didymin and naringin and the role of naringin have been reported for its antidiabetic effects(Pari&Suman,2010) .Riazet al. (2013) suggest that Citrus limon have phytochemical and other essential nutrients which have reduced blood glucose levels in alloxan induced diabetic rats as compared to diabetic control, that works synergistically in combination. So it may be concluded that the response of *Citrus limon* on blood glucose may be due to presence of flavonoids in these juices and a synergistic effect is observed by their combination. Naim*et al.* (2012) mentioned that the hexane extracts of lemon peel showed antidiabetic activity comparable to that of glimepiride, It can thus be inferred that the extract of lemon peel possesses significant antidiabetic activity. Antihyperlipidemic activity The *Citrus limon* juice (1ml/kg/day) for rabbits revealed a significant reduction in serum cholesterol, triglycerides and LDL levels and resulted in an increase in HDL, which suggests that the hypo cholesterolemic effects of *Citrus limon* juice may be due to its antioxidant effect (Khan*et al.*,2010). Antihypertension activity In a survey of hypertensive patients in a local region of northern Turkey, 156 (72.5%) of hypertensive patients were using alternative therapy that include lemon juice and 86 patients (40%) were drinking lemon juice (Adibelli*et al.*,2009) .

Khama'al(2014) refers to significant decrease ($p < 0.05$) in the level of each of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and significant increase ($p < 0.05$) in the level of estradiol hormone (E_2)for both concentrations and dosing periods and two extracts compared with the control group.

MATERIALS AND METHODS

Induction of Diabetes in Rats by Alloxan

Rats were made diabetic by a single injection of 150mg/kg of alloxan monohydrate dissolved in saline to overnight fasted animals, It is followed by 0.5 ml of 25% Dextrose after 2 hours of alloxan and 5% Dextrose solution ad libitum for next 24hours, After 7 days of alloxan, blood samples were pull from rat tail vein and blood glucose levels were evaluated in all animals, animals with blood glucose level ≥ 200mg/dl (Diabetic) were selected for study (Ravinder & Devender, 2011).

Hot Aqueous Extract

20 gm of powdered sample was suspended in 200 ml of distilled water. Extraction was done at 70˚C for 30 minutes, followed by filtering of the extracts using Whatman filter paper No.1. Extracts were then evaporated at 45˚C by rotary evaporator to form a paste, and further transferred in to sterile bottles and refrigerated at 4˚C until use (Nassem et al.,1998; Patil & Patil 2012).

Experimental Design

Experimental rats were divided into five groups of six animals each and treated for 30 days as follows.

Group A - Normal control (administration normal salin)

Group B - Diabetic control (injected with alloxan)

Group C - Diabetic+ Amyral 1mg/kg b.wt)

Group D - Diabetic+hot aqueous Extract of *Citrus lemon* seed (500 mg/kg b.wt)

Group E- only hot aqueous Extract of *Citrus lemon* seed (500 mg/kg b.wt)

Blood samples were collected from ratheart vein and blood glucose levels are estimated using one touch glucometer.

RESULTS

The results in table 1 showed a significant decrease ($p<0.05$) in levels of (Hb,RBC and WBC) in group treated with alloxan compared to control. Treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant increase in levels of (Hb, RBC and WBC) compared with alloxan group.

The other groups treated with lemon extracts at concentration500 mg/kg of body weight, the results showed a significant increase ($p<0.05$). In levels of (Hb,RBC and WBC) compared with alloxan**.**

Table 1: Effect of Seed Citrus Limon on Some Hematological Parameters Hb, RBC and WBC in Animals Treated with All oxan

Estimation of (WBC, RBC, HB) Count			Parameter
Hb (mg/dl)	**RBC ($X*10^6$) / µl**	**WBC ($X*10^3$) / µl**	**Groups**
14.70± 0.163	6.948 ±0.0465	7.670± 0.2499	**Positive controls**
12.43±0.427	6.450±0.2426	3.488 ±0.1841	**Negative controls**
14.73±0.096	7.875 ±0.1047	12.950±0.2380	**Only extract of *Citrus limon***
14.43 ±0.299	7.543 ±0.2771	8.540 ±0.3122	**Alloxan+extract of *Citrus limon***
13.35 ±0.129	6.813± 0.0050	5.813 ±0.0050	**Alloxan(Amyral)+**
0.18	0.14	0.18	**(P<0.05L.S.D)**

Meen± SD

Effect of Seed Citrus Limon on Some Biochemical Change Glucose

The results in figure 1 showed a significant increase ($p<0.05$) in levels of (Glucose) in group treated with alloxan compared to control, treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant decrease in levels of Glucose compared with alloxan group.

The other groups treated with lemon extracts at concentration500 mg/kg of body weight, the results showed a significant decrease ($p<0.05$).in levels of (Glucose) compared with alloxan.

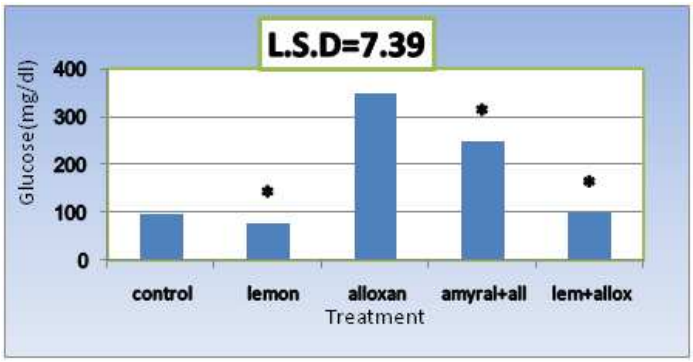

Figure 1: Effect of Aqueous Lemon Extract on Glucose in Rats Treated with Alloxan

Effect of Seed Citrus *Limon* on Some Biochemical Change (Cholesterol Triglyceride)

The results in figure 2 showed a significant increase($p<0.05$) in levels of (Cholesterol, Triglyceride) in group treated with alloxan compared to control, treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant decrease in levels of Cholesterol and Triglyceride compared with alloxan group. The other groups treated with lemon extracts at concentration500 mg/kg of body weight, the results showed a significant dcrease ($p<0.05$).in levels of (Cholesterol, Triglyceride) compared with alloxan.

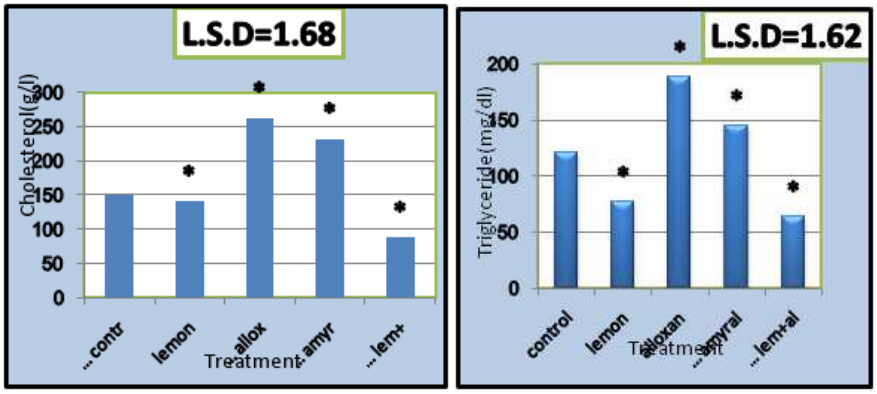

Figure 2: Effect of Aqueous Lemon Extract on Cholesterol and Triglyceride in Rats Treated with Alloxan

Effect of Aqueous Lemon Extract on HDL LDL in Rats Treated with Alloxan

The results in figure 3 showed a significant increase($p<0.05$) in levels of (LDL) in group treated with alloxan compared to control, Treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant decrease in levels of LDL compared with alloxan group.

The other groups treated with lemon extracts at concentration500 mg/kg of body weight, the results showed a significant decrease ($p<0.05$).in levels of (LDL) compared with alloxan while showed a significant decrease($p<0.05$) in levels of (HDL) in group treated with alloxan compared to control, Treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant Increase in levels of HDL compared with alloxan group.

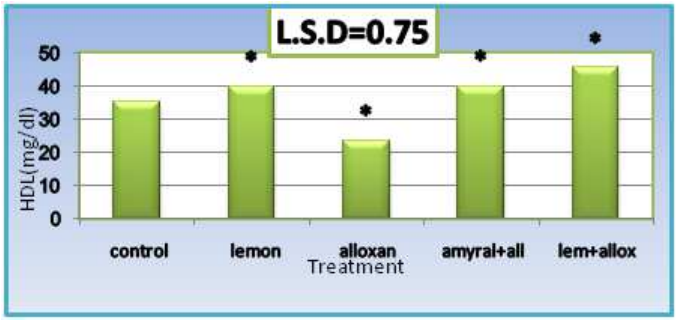

Figure 3

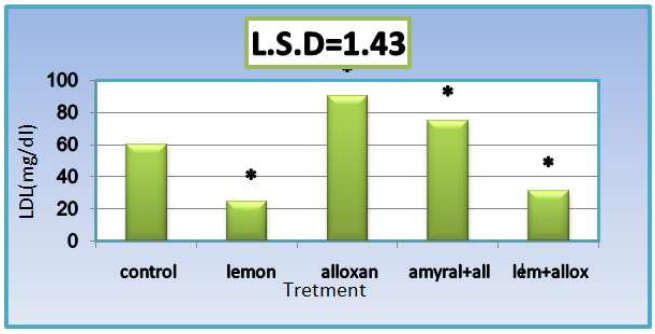

Figure 4: Effect of Aqueous Lemon Extract on LDL and HDL in Rats Treated with Alloxan

Effect of Aqueous Lemon Extract on HDL, LDL in Rats Treated with Alloxan

The results in figure 4 showed a significant increase($p<0.05$) in levels of (AST,ALT) in group treated with alloxan compared to control, Treated the animals with ECl at concentration500 mg/kg of body weight for one month showed a significant decrease in levels of (AST,ALT) compared with alloxan group. The other groups treated with lemon extracts at concentration500 mg/kg of body weight, the results showed a significant dcrease ($p<0.05$).in levels of (AST,ALT) compared with alloxan.

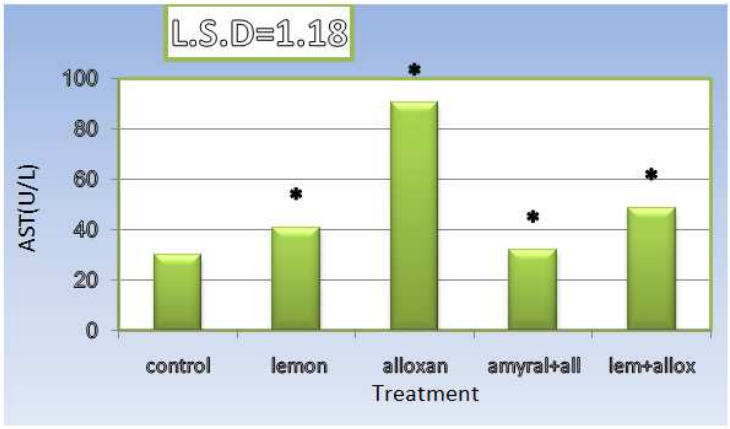

Figure 5

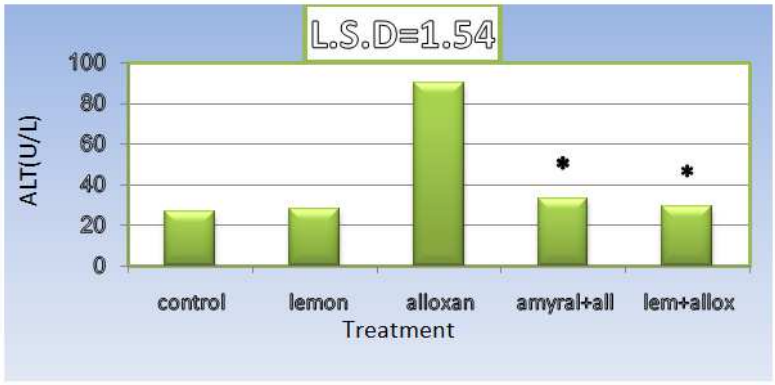

Figure 6: Effect of Aqueous Lemon Extract on AST and ALT in Rats Treated with Alloxan

DISCUSSIONS

Alloxan is a chemical agent to induce diabetes mellitus by selective damage effect on pancreatic beta cells. that suppresses the immune system that lead to decrease levels of (WBC,RBC,HB) (Oyedemi et al.,2010). But when administration of the extract at 500 mg/kg The level of (WBC,RBC,HB) was slightly increased due to antioxidant activity of lemon extracts that acts as scavenge for free radicals that responsible for distraction all blood cells (Pariet al.,2010).

In this study shows the effect of alloxan is considered as major cause of hyperglycemia due to free radicals generation (Kawahito et al.,2009) also shows the effect of seed Citrus limon to decrease blood glucose level and improve in plasma insulin in diabetic animals treated with ECl Citrus limon which acts as strong antioxidant, also presence naringin have been reported for its antidiabetic effects(Violiet al.,2010) also alloxan effect on cholesterol levels in diabetic animals due to increase obsorption of cholesterol from intestine that stimulate insulin decrease (Hori et al ., 2004). The lemon contain saponin and lectin that possess shypolipidemic effect that similar action of Salvia officinalis (Alayan, 2006).Also showed increase levels of (triglyceride, LDL)and decrease levels of (HDL) in diabetic rat when administration of ECl seed showed may change occur in levels due to presence Hesperidin is the most important flavanone of Citrus sp., significantly increased high density lipoprotein(HDL) and lowered cholesterol low density lipoprotein levels(LDL), and triglyceride plasma levels (Monforte et al.,1995).

Administration of alloxan caused effectiveness in liver function tests such(AST,ALT)alanine aminotransferase

and aspartate aminotransferase are increased in individuals with insulin resistance and the metabolic syndrome (Hanley et al.,2004) .when treated diabetic rats with ECl that decrease the level of (AST,ALT) because the lemon contain phytochemicals such asflavones, poly phenols) (Capasso et al., 2003).

Statistical Analysis

Data were expressed as (mean ± SD) of fife replicates and were subjected to one way analysis of variance (ANOVA). Means were separated by the Duncan multiple test Values were considered statistically significant at $P < 0.05$.

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