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The Effect of Cinnamomum verum and saxagliptin on some biochemical parameters of the liver in male rats induced diabetes by alloxan

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ABSTRACT

Diabetes mellitus is a major global health concern in the current study which is chiefly characterized by the rise in blood sugar levels or hyperglycemia. To study the antidiabetic activity of aqueous extract of Cinnamomum verum in alloxan induced diabetic albino rats. The aqueous extract of cinnamon 100mg/kg and 200mg/kg was studied alone and in combination with conventional oral antidiabetic drugs like saxagliptin 5mg/kg in alloxan-induced diabetic albino rats measuring the level of liver enzymes Alanine transaminase, Aspartate aminotransferase. The study included 56rats divided into seven groups (8for each group) with weights ranging from 200-250mg, the first group was as a control group, the second group was injected with alloxan 120 /kg/b.w. and nicotinamide 50 mg/kg/b.w. The third diabetic group received treatment with 5 mg/kg/ b.w. of saxagliptin drug. The fourth diabetic group received treatment with 100 mg/kg/b.w. of cinnamon. The fifth diabetic group received treatment with 200 mg/kg/b.w. of cinnamon. The sixth diabetic group received treatment with 100 mg/kg/b.w. of cinnamon and saxagliptin (5 mg/kg/ b.w.). The seventh diabetic group received treatment with 200 mg/kg/b.w. of cinnamon and saxagliptin (5 mg/kg/ b.w.). The animals were scarified and the heart's blood was extracted. where the serum was isolated to study the biochemical parameters of liver enzymes. The study's findings demonstrated an increase in the effectiveness of liver enzymes as a result of the injection of alloxan, but after treatment with cinnamon and saxagliptin, the level of these enzymes decreased in the treatment groups and also demonstrated that 30 days treatment with saxagliptin (5mg/kg) orally exhibited a significant ($P \leq 0.05$) decrease in AST, ALT when compared to diabetic rats but there are no significant differences when compared with cinnamon treatment groups (100 and 200mg/kg) when administration alone. Also, the study show that the aqueous extract of cinnamon produced a significant lower the liver enzymes (ALP, AST) and the combination of Cinnamon with saxagliptin when given for 30 days in alloxan induced diabetic albino rats caused more significant reduction in liver enzyme level than either drug is given alone. Combination of aqueous extract of Cinnamon (100 and 200mg/kg) with saxagliptin (5mg/kg) orally for 30 days significantly ($P<0.05$) enhanced the livers enzyme lowering when compared to cinnamon (100 and 200mg/kg) and saxagliptin (5mg/kg) when administration alone and to diabetic group but there are no significant differences when compared with control group. This indicates that cinnamon enhances the therapeutic efficacy of saxagliptin when given in combination..

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycaemia due to insulin deficiency, or insulin resistance, or both. Hyperglycaemia occurs when cells become unable to utilize glucose and/or the liver and skeletal muscles cannot store glycogen [1]. There are two basic types of diabetes mellitus: type 1 and type 2. Insulin-Dependent.Diabetic Mellitus (IDDM) Type 1, often known as juvenile diabetes, mainly affects children and young people under the age of 40. A lack of insulin is the major cause of type II diabetes in people over the age of 40 who have non-insulin-dependent diabetes mellitus (NIDDM), a form of diabetes caused by the entire or partial regeneration of beta cells in the pancreas. It is because of this that T2DM (90–95 %) is the most common kind of DM worldwide. Diet and oral hypoglycemic medicine may be used to control this disease [2].

Currently, diabetes is a global epidemic. The number of persons globally with diabetes is predicted to climb significantly in the next several years [3]. In addition to conventional pharmaceuticals, WHO might consider using natural goods such as dietary supplements and herbal remedies (WHO). As many as 1,200 different species of herbal remedies may be used to treat type 2 diabetes. People throughout the world have long relied on natural remedies like herbs and plants to treat and prevent ailments. Plants, microorganisms, marine life, vertebrates, and invertebrates are only some of the various sources of this chemical [4]. When it comes to new medicines, there is no limit to the number of chemicals found in natural products like plant extracts [5].

There are some medicinal plants have been declared in diabetes treatment worldwide and have been used

experimentally as antidiabetic remedies. Antihyperglycemic effects of these plants are attributed to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes [6]. It belongs to the Lauraceae family, Cinnamomum zeylanicum. It is one of the most used and oldest spices in human history as a spice and flavoring component. If you're looking to improve your health, this is one of the healthiest spices you can utilize [7].

Saxagliptin one of the utmost new Dipeptidyl peptidases 4 (DPP 4) drugs. The DPP 4 inhibitor saxagliptin has been used for the treatment of renal, heart, pancreatic and retinal disorders [8]. DPP-4 inhibitors have been shown to improve brain function by reducing mitochondrial dysfunction, insulin resistance, inflammation and apoptosis [9]. DPP 4 inhibition has extra pancreatic protective effects against diet induced adipose tissue inflammation and hepatic steatosis (10). Dipeptidyl Peptidase-4 (DPP-4) inhibitors are the newer class of compounds that were approved in 2006 for the treatment of T2DM (11).

Due to the lack of studies on this type of important medicinal plants (Cinnamomum verum), the current study was planned, which aims to demonstrate the effect of the aqueous solution of the cinnamon by using two doses (100 and 200 mg/kg) and their combination with drug (saxagliptin) on the liver of laboratory adult male rats in which diabetes is induced and knowing the preventive effect on it.

2 MATERIALS AND METHODS

2.1 The experimental animals

The study was performed using 56 male of albino rats Rattus norvegicus, Sprague Dawley strain were used with average weight (200-250g) aged between (3-4 months). Prior to the start of the trial, the animals had a one-week acclimatization period. The animals were kept in conventional conditions both before and during the experiment, with a temperature of 22±2°C and a consistent 12/12 h light-dark cycle. Standard pellets and unlimited tap water were made available to the rats without restriction

2.2 Induction of type 2 diabete

After a 12-hour overnight fast, the rats received an intraperitoneal injection of freshly produced alloxan monohydrate and nicotinamide (Sigma, USA; 120 +50 mg/kg b.w.) to cause type 2 diabetic mellitus.In regular saline. Animals were deemed diabetic and chosen for the following studies after 72 hours if their fasting blood glucose levels were greater than 200 mg/dL. [12].

2.3 Cinnamomum verum aqueous extract preparation

Cinnamon plant (Cinnamomum verum) was bought from the popular market in AL-Kut city/wasit province,Iraq. Preparation dosing of 100mg/kg of cinnamon verum ;100mg of cinnamon powder was dissolved in 1ml of distilled water, then the solution was administered orally by stomach tube as 0.5ml/kg of B.W. Preparation dosing of 200mg/kg of cinnamon; 200mg of cinnamon powder was dissolved in 1ml of distilled water, then the solution was administered orally by stomach tube as 0.1ml/100g of B.W[13].

2.4 Preparation of Saxagliptin drug

Stock solutions were prepared by dissolving one tab of 5 mg saxagliptin by ethanol within 70 ml distilled water, then the drug was administered orally by stomach tube as 0. 1 ml /100g of B.W [14].

2.5 The Experimental design

The animals were divided at randomly into seven main groups (8 male rats in each group).

1-Group one {non treated, non-diabetic (Type 2 Diabetes Miletus (T2DM)} normal negative control group, received distilled water, with normal diet. For a period of 30 days.

2- Group two (T2DM, non-treated) T2DM induced by intraperitoneal single dose injection of alloxan (120 mg /kg/day) + Nicotinamide 50 mg / kg.

3-Group three (T2DM, treated orally with saxagliptin drug 5 mg\kg for a period of 30 days)

4-Group four (T2DM, treated orally by oral gavage with cinnamon extract 100 mg / kg for a period of 30 days).

5-Group five (T2DM, treated orally with cinnamon extract 200 mg /kg for a period of 30 days).

6-Group six (T2DM, treated orally with saxaglibtin 5mg\kg and cinnamon extract 100 mg / kg for a period of 30 days).

7-Group seven (T2DM, treated orally with saxaglibtin 5mg\kg and cinnamon extract 200 mg / kg for a period of 30 days).

2.6 Collection of Blood Samples and tissue

Blood samples were obtained by heart puncture; by using test tubes with no anticoagulant and blood samples were collected to allowable standup and coagulating. Serums were separated from coagulated blood samples by

centrifuge at 1000 round per minute (rpm) for 15 min, then samples of serum were kept in a freezer at -20 Ċ˚for the purpose to measuring the level of liver GOT, GPT by Elisa according to commercial kits instructions (My BioSource USA), and Scarifying animals were done by chloroform.

2.7 The Statistical Analysis

The Statistical Analysis System-SAS (2012) program was used to detect the effect of difference factors in study parameters. Least significant difference (LSD) test and Analysis of Variation (ANOVA) were used to statistical compare between means of obtained results.

Result And Discussion

When compared to the negative control group, the levels of the enzyme's alanine aminotransferase (ALT/GPT) and aspartate aminotransferase (AST/GOT) were significantly higher in diabetic rats (P≤0.05). AST and ALT values were significantly (P≤0.05) lower after cinnamon and saxagliptin administration compared to the diabetes control group according Table-1.

Table (1): Liver enzyme U/L in induced diabetic rats' groups dosed orally during the thirty days of experiment

Parameters / Groups	Mean ± SE	
	ALT(GPT) (U\L)	AST(GOT) (U\L)
Control group(G-)	72.12±1.126 a	145.88±0.835a
Positive group (G+)	112.88±0.835 c	225.88±0.835c
Saxaglptin group	83.25±1.165 b	191.38±1.188 b
Cinnamon 100mg	82.62±2.264 b	188.88±0.835 b
Cinnamon 200 mg	82.88± 2.031 b	186.6±1.188b
Saxagliptin + Cinnamon 100mg	71.62±1.408 a	147.38±1.847a
Saxagliptin + Cinnamon 200mg	72.50±1.927 a	148.00±1.414a
LSD value	**1.642**	**5.483**

Values are expressed in Means ± SD. Values superscripted by different letters within the same column are significantly (P ≤0.05) different.

Results of present study clearly indicate that 30 days treatment with saxagliptin (5mg/kg) orally exhibited a significant (P≤0.05) decrease in AST, ALT when compared to diabetic rats but there are no significant differences when compared with cinnamon treatment groups (100 and 200mg/kg) when administration alone.

The results of present study show that the aqueous extract of cinnamon produced a significant lower the liver enzymes (ALP, AST) and the combination of Cinnamon with saxagliptin when given for 30 days in alloxan induced diabetic albino rats caused more significant reduction in liver enzyme level than either drug is given alone.

Combination of aqueous extract of Cinnamon (100 and 200mg/kg) with saxagliptin (5mg/kg) orally for 30 days significantly (P<0.05) enhanced the livers enzyme lowering when compared to cinnamon (100 and 200mg/kg) and saxagliptin (5mg/kg) when administration alone and to diabetic group but there are no significant differences

when compared with control group. This indicates that cinnamon enhances the therapeutic efficacy of saxagliptin when given in combination.

Obviously, alloxan causes a significant elevation in glucose concentrations when administered to rat compared to the control. The results of the current study showed that GPT and GOT levels in the serum of male albino rats increased after alloxan-induced diabetic mellitus, which is consistent with the study's findings [15, 16, 17] that the reason for this increase may be due to damage to the membranes of hepatocytes due to increased lipid peroxidation and an increase in the concentration of free radicals resulting from diabetes mellitus, which leads to the leakage of enzymes into the blood serum [18]. Alloxan may have a role in increasing hepatic necrosis and damage to hepatocytes, which gives evidence of the high toxicity of alloxan and the liver attempts to remove the alloxan toxicity, as in this case, the enzymes rise of GPT and GOT is consistent with those indicated by other studies [19, 20]. These two enzymes may have increased levels due to the hepatocytes growing larger and the endoplasmic reticulum being stimulated to manufacture more of the enzyme to accommodate the growth of the cell [21]. It may be attributed to the fact that alloxan increased blood sugar, leading to increased oxidative stress and the formation of ROS, which led to oxidation and necrosis of fats in the membranes of liver cells, which led to an increase in the effectiveness of these enzymes in the liver [22].

Saxagliptin is a selective, reversible, and competitive dipeptidyl-peptidase-4 (DPP-4) inhibitor. The incretin hormones, GIP (glucose-dependent insulinotropic polypeptide) and GLP-1(glucagon-like peptide-1) are released in a glucose-dependent manner in response to a meal. These hormones, released from the small intestine, stimulate the pancreas to secrete insulin as well as decrease the secretion of glucagon. DPP-4 rapidly inactivates the incretin hormones, decreasing their duration of action. It is present within the endothelium of various organs and has enzymatic activity in circulating plasma (23,24). Inhibition of DPP-4 is an attractive therapeutic mechanism which results in increased plasma concentrations of endogenous GLP-1. Saxagliptin inhibits DPP-4, precipitating an increased concentration of these endogenous hormones that ultimately lowers fasting and postprandial glucose levels in patients with type 2 diabetes (25,26).

The experimental results proved a significant hypoglycemic and lipid-lowering effects for treatment by cinnamon in rats. Oral administration of cinnamon extract for 21 days in alloxan-induced diabetic rats resulted in a significant decrease in the blood glucose level [27]. Cinnamon increased the insulin sensitivity and glucose uptake in adipocytes. The hypoglycemic effects of cinnamon extract are through an improvement of glucose uptake by stimulating the activity of insulin receptor kinase and glycogen synthase as well as insulin receptor autophosphorylation [28]. This can be accounted for the blood glucose reduction through glucose utilization. It was suggested that improving the metabolic syndrome by cinnamon extract is through regulating the genes related to carbohydrate metabolism and lipogenesis [29]. Glucose transport is facilitated by glucose transporters (GLUT) across the cell membrane [30]. GLUT4 dependent glucose transport is considered insulin dependent [31] as insulin signal transduction pathway mediates the transcription and intracellular movement of GLUT4 gene product into the cytoplasmic membrane. So, any drug facilitates GLUT4 translocation in adipose tissue can improve carbohydrate metabolism and it is preferable to be a natural product as cinnamon. The cinnamon extract or its derivative, dihydrocinnamic acid, enhanced the GLUT4 gene expression in animal adipose tissue [32] Moreover, cinnamon extract enhanced GLUT4 contents in the cytoplasmic membrane that it facilitates glucose entrance to the cell [33].

Cinnamomum verum belongs to the family Lauraceae and possesses significant ant allergic, antiulcerogenic, antipyretic and anesthetic activities [34]. Several biological activities, such as peripheral vasodilator, antitumor, antifungal, cytotoxic and antimutagenic,have been attributed to cinnamaldehyde [35]. Serum AST and ALT activities were used as a marker of liver damage. CC14 produces an experimental damage [36]. The toxic metabolite .CC13 radical is produced by cytochrome p450 which further reacts with oxygen to produce trichloromethyl peroxy radicals. These radicals bind covalently with the macromolecule and cause peroxidative degradation of lipid membrane of the liver. The reduction of AST and ALT activities by the extracts is an indication of repair of hepatic tissue damage induced by CC14. This is in agreement with Thabrew et al. [37]. who found that serum transaminases returned to normal activities with the healing of hepatic parenchyma and regeneration of hepatocytes, The cinnamon extract induced suppression of increased ALT and AST activities. Thus, administration of ethanolic or aqueous extracts of cinnamon revealed hepatoprotective activity against the toxic effect of CCl4, which is also supported by histological studies.Oxidative stress induced due to the generation of free radicals and/or decreased antioxidant level in the target cells and tissues has been suggested to play an important role in carcinogenesis [38]. Lan et al. [39] stated that 50% of acetone extract of cinnamon contained high levels of phenolic groups. Scavenging of free radicals is one of the major antioxidation mechanisms to inhibit the chain reaction of lipid peroxidation. Reduced lipid peroxidation was revealed by a significant decrease in MDA level in groups pretreated with water or ethanol extracts,simultaneously with a significant elevation in SOD and CAT activities.

Our results are somewhat in accord with the findings of Abd-El-Rahman and colleagues (2010) which they reported that oral application of extract and powder of cinnamon in rats with type 2 diabetes mellitus decreased

the levels of liver enzymes including AST [40]. Additionally, the results of the study of Amin and colleagues (2009) on the effect of cinnamon on fatty liver disease in rats are also along with these findings [41].

Polyphenols also have antidiabetic potency by increasing the secretion of GLP-1 which indirectly stimulates pancreatic langerhans islets to regenerate beta β cells. Flavonoids can also increase the antioxidant capacity of beta cells through both enzymatic and non-enzymatic pathways. The inhibited oxidation process prevents the formation of ROS and lipid peroxidation which can cause autophagy, apoptosis and necroptosis as well as provide opportunities for normal β cells to carry out its physiological functions, namely producing insulin which plays a role in the uptake of blood glucose into body cells [42]. Ali and Bakr show that the cinnamon verum extract was characterized by its high phenolic and flavonoid contents, which had an important role as antioxidants. The high content of these bioactive components may play a significant role as protective bioingredients against liver cirrhosis in rats treated with carbon tetrachloride. Several previous studies demonstrated the relationship between the biomarker assay and the changes in histology of the liver [43]. Deterioration of liver cells leads to loss of function, and change the permeability of cell membranes resulted in leak of enzymes such as ALT and AST in the extracellular space followed by the emergence of odema and infiltration [44 ,45,46; 47]. Fat peroxide is shown when number of free radicals presented in high amount comparing to antioxidant level in the body, therefore, the MDA may be raised. These peroxides bind to sensitive body compounds such as double bonding of membranes and cause damage [48,49]. The water extract of cinnamon raised the total protein levels toward the normal levels in the blood serum, thereby protecting the liver. This may be due to stimulating protein synthesis and accelerating the regeneration and production of liver cells [50,51]. Therefore, histopathological consequence is in harmony with Eidi et al., [52]. Who describe that, pretreatment of experimental rats with cinnamon extract significantly enhanced the construction of hepatic cells and moderated hepatotoxicity induced by the CCl4...

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