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Evaluation the Anti-Diabetic Activity of Cherry Laurel (*Laurocerasus officinalis*)

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Abstract: *Purpose*: Cherry laurel has been used as an anti-diabetic drug. In this study, we aimed to evaluate its anti-diabetic activity at standard living conditions and under stress by an experimental study.

Material and Method: Forty Wistar-Albino rats weighing 300–350 grams were used in this study. Four groups were structured: control, diabetic, glibenclamide and cherry laurel extract. Streptozotocin (50 mg/kg) was injected to induce diabetes. Cherry laurel extract was obtained from the seed of the fruit. Routine blood glucose, insulin, pre- and intra-anesthesia blood glucose levels were measured and compared. The One-way ANOVA followed by Duncan post-hoc test was used for statistical analysis.

Results: After the second week of the experiment, Extract 300 and Extract 600 groups had the lower glucose levels ($p<0.05$). Also, insulin levels measured at the last week of the study revealed that Extract 300 and Extract 600 groups had the highest results ($p< 0.01$). Glucose levels under stress conditions significantly changed for Extract 300 and glibenclamide group ($p<0.05$). Glucose level changed more obviously in the Extract 600 group ($p<0.001$) that means irregularity.

Conclusion: Cherry laurel extract exhibits an anti-diabetic effect, with administration leading to elevated insulin levels, and regulating glucose levels under stress conditions like anesthesia. These preliminary results indicate that further evaluation is warranted.

Keywords: Anti-diabetic, anesthesia, cherry laurel extract, herbal treatment, ketamine, rat.

INTRODUCTION

Diabetes mellitus (DM) affects 3% of the global population and its prevalence is increasing [1, 2]. The disease originates from a disorder in glucose homeostasis [3]. Effective drugs that aid the control of glucose levels are very important in the prevention of these complications and in alleviating the symptoms of DM.

Drugs such as glibenclamide stimulate the secretion of insulin and can be effective in the treatment of DM [4]. Glibenclamide, which belongs to the sulphonylurea class of drugs, is one of the most widely used oral anti-diabetic drugs. Nevertheless, anti-diabetic drugs like sulphonylurea have side effects [5]. While these side effects may be maintained at levels considered acceptable, the search for new substances that do not exhibit side effects and that have higher efficacy remains an important research area.

Rural herbal remedies have long offered excellent starting points in the search for new chemotherapeutic agents and drugs [1]. Successes in the field have stimulated increasing interest in complementary medicine [5].

Here, we present our investigation on cherry laurel (*Lauracerasus officinalis)* for its anti-diabetic activity and its effect on insulin levels. This fruit which is grown in the central Anatolian region by the Black Sea in Turkey, is used as an anti-diabetic remedy by the local population [6]. No clinical or experimental reports have been published previously on the activity of this herb. We used seed of the cherry laurel to evaluate the anti-diabetic activity. The focus of this study was to confirm the activity of cherry laurel on glucose homeostasis to establish if further studies are warranted to elucidate the active components of the herb. Also, we added glucose measurement under stress condition to figure out the regulative effect of the treatments under stress. We suggested that the most measurable circumstances for a stress situation was anesthesia. So, we measured glucose levels during anesthesia of rats.

MATERIALS AND METHODS

The approval of a local ethical committee and the sponsorship of the scientific research project committee of Gaziosmanpasa University were obtained. After this, streptozotocin (STZ) from Sigma-Aldrich®, glucose from Boehringer Mannheim commercial kit and insulin were obtained from Linco Elisa commercial kit for rats. Rats were used from our own experimental research laboratory.

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Experimental Group Preparation

Four experimental groups were formed. Adult male Wistar-Albino rats weighing 300–350 g were used in each group. A total of 40 rats were used with 10 individuals in each group. Rats were housed under standard environmental room conditions and fed ad libitum.

Experimental Groups

1- Control group: healthy rats were used to study control blood glucose and insulin levels for comparison.

2- Diabetic group: STZ was administered using intra-peritoneal injection to induce diabetes. No diabetes treatment was administered.

3- Glibenclamide group: STZ was administered using intraperitoneal injection to induce diabetes, and 600 μg/kg/day of the anti-diabetic drug glibenclamide was given orally each day.

4- Extract group (Extract 300 and Extract 600): STZ was administered using intraperitoneal injection to induce diabetes. The group was split into two subgroups that were given cherry laurel extract twice at two equal doses. The first subgroup was treated with 300 mg/kg/day cherry laurel extract (Extract 300), while the other subgroup was treated with 600 mg/kg /day extract (Extract 600) on each day of the study.

Diabetes Induction

A single dose of STZ (50 mg/kg) was administered using intraperitoneal injection. Four days after administration, blood glucose levels were measured. DM was diagnosed if the blood glucose level was found to be higher than 240 mg/dl after 3 hours of fasting.

Cherry Laurel Extract Preparation:

The extract was prepared from cherry laurel seeds. The seeds (100 g) were first pulverized, then soaked in 250 ml water for 2 h. The mixture was then stirred at 60–65°C for 30 minutes. The aqueous product was transferred into another container and the residue was handled again by the same procedure. The procedure was repeated until the supernatant was clear. The final extract was filtered using a gauze sponge. Finally, the filtrate was dried 40°C to give the final extract.

Glibenclamide and cherry laurel extracts were given to rats using oro-gastric lavage tubes [7].

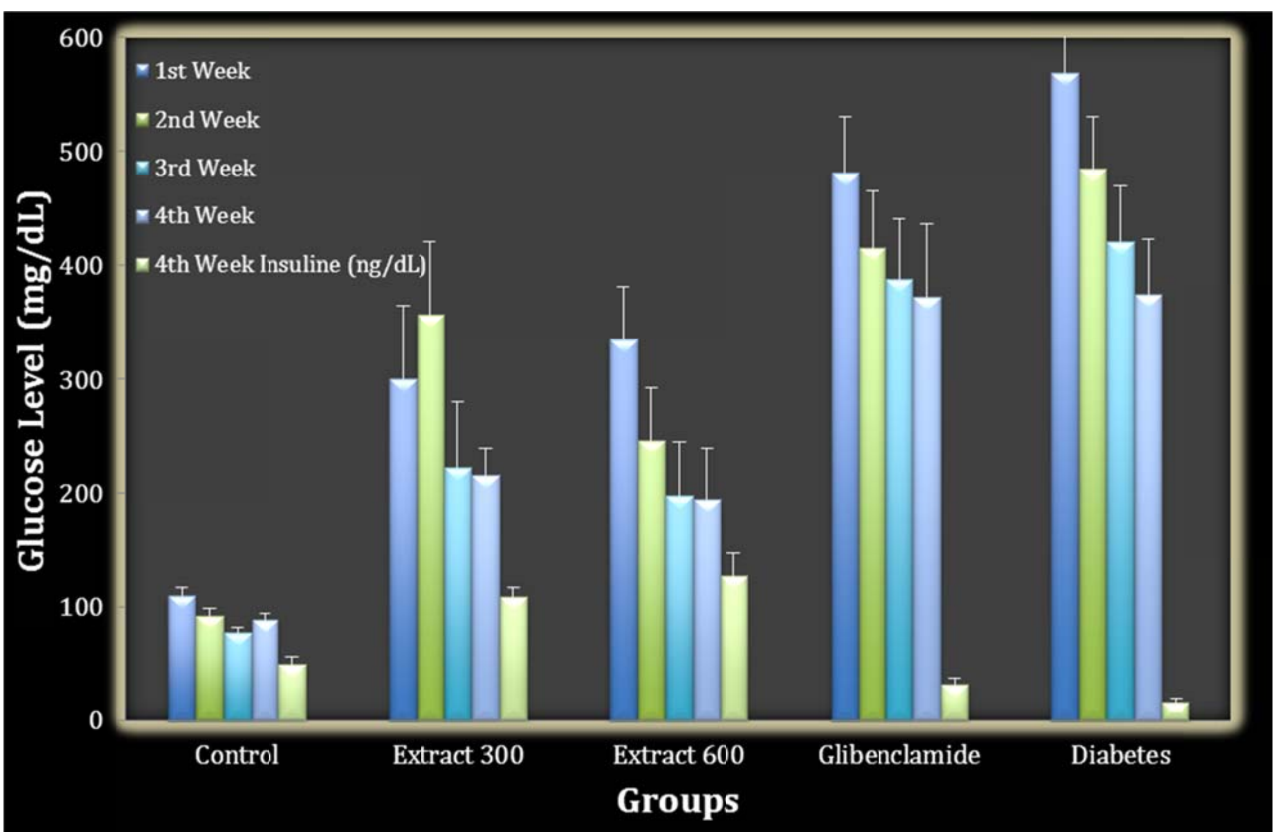
Rat Environment

Rats were housed at 24°C and a 12 h cycle of night and day were maintained during the experiment. Standard nutritional solution was given, with the rats feeding ad libitum. Rats were monitored for 30 days. Glibenclamide was given as a single dose while the cherry laurel extract was given twice each day in divided equal doses. Blood was taken for glucose testing each week, and was taken 30 minutes after feeding. Spectrophotometric evaluation was used to measure glucose content.

Glucose Determination

Spectrophotometric evaluation was used to measure glucose content. NADP reduction principles are used for

Table 1. Glucose Levels During 4 Weeks Time and Insulin Levels of the Groups at the Final Measurement



glucose determination. Glucose and insulin levels were compared with the levels in control group.

Insulin levels were measured at the end of the study. The experiment was ended by sacrificing the animals on the 30th day, by the intra-peritoneal injection of 150 mg/kg pentobarbital sodium.

Anesthesia and Blood Sampling

On the 30th day, blood was sampled before and during anesthesia. First, blood was sampled from fed rats, then doses of drug and extract were given. After then fasting for 2 hours, blood samples were obtained from the rats. Anesthesia was then performed by intra-peritoneal injection of a mixture of ketamine and xylazine (ketamine 100 mg/kg and xylazine 10 mg/kg). Anesthesia levels were tested by reflexes analysis. Once optimum anesthesia had been achieved, a final blood sample was taken (around 20 mins after anesthetic injection).

Statistical Analysis

The One-Way ANOVA followed by Duncan posthoc test was used for statistical analysis of glucose and insulin levels, and *harmonic distribution* was used to evaluate unequal distribution.

RESULTS

After STZ injection, three rats in the cherry laurel extract group (two Extract 600 and one from Extract 300) and two rats in the glibenclamide group died of unknown causes before the onset of treatment.

After the second week of the experiment, Extract 300 and Extract 600 groups had the lower glucose levels than glibenclamide and diabetes groups according to control groups ($p<0.05$). Table **1**. Also, insulin levels measured at the last week of the study was shown in Table **1** near the last week glucose measurement to reveal a comparison. Extract 300 and Extract 600 groups had the highest results ($p< 0.01$).

For stress condition measurement, the glucose levels of pre- and intra-anesthesia rats for fed and fasted rats are compared in Table **2**. Only, diabetes group had regular blood glucose levels. Extract 300 and glibenclamide group had significance ($p<0.05$). Glucose level changed more obviously in the Extract 600 group ($p<0.001$).

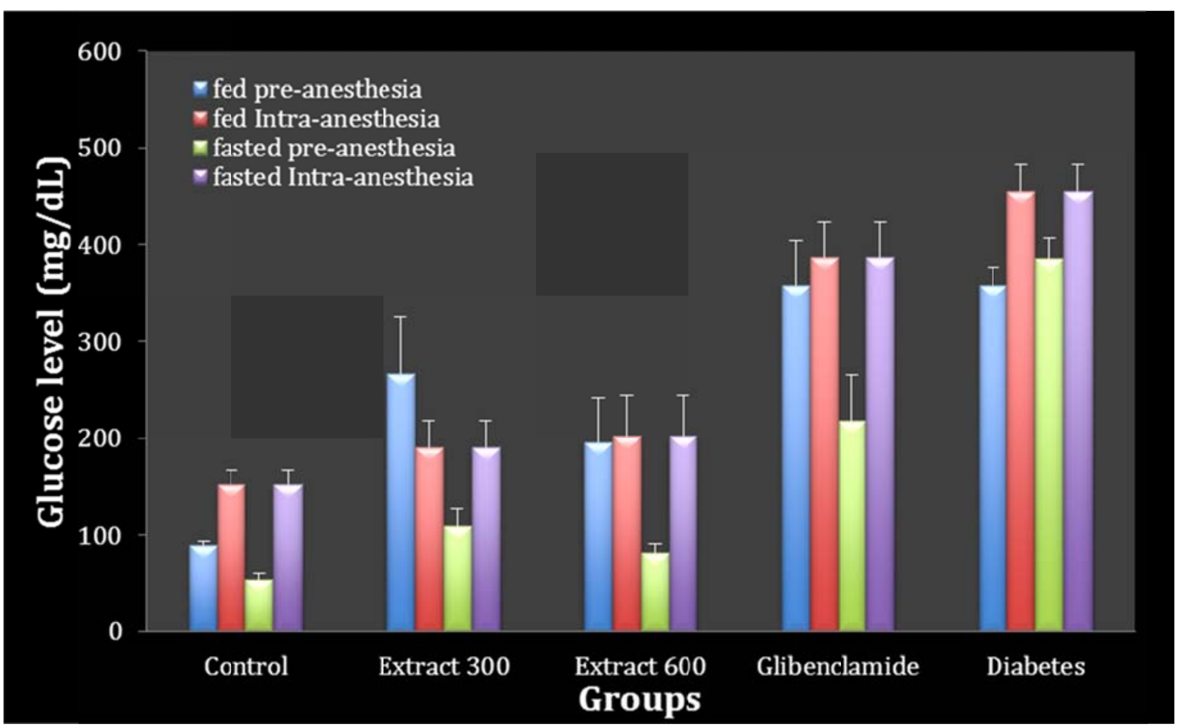
DISCUSSION

Cherry laurel (*Laurocerasus officinalis*) is a fruit found in the Black Sea region of Anatolia and its ethnopharmacological use has been practiced for the treatment of diuresis, diabetes, stomach ulcers, bronchitis, eczema and hemorrhoids [6]. In literature, there has not been a study analyzing the anti-diabetic effect of cherry laurel.

In our study, cherry laurel was investigated for its anti-diabetic efficiency by comparison with a widely used anti-diabetic drug, glibenclamide. It was found that glucose levels were better maintained by the extract than glibenclamide. In addition, insulin concentrations, measured at the end of the experiment, were found to be higher in the extract group than for other groups. Glucose stability during anesthesia also confirmed the regulative effectiveness of the extract. Our experimental indicated that cherry laurel imparts this activity by promoting insulin secretion. We therefore propose that the efficiency of cherry laurel for DM can easily be foreseen by this study and the extract deserves further attention towards its development as an anti-diabetes drug.

Anti-diabetic drugs have previously been developed from herbal sources [3]. Many indigenous Indian medicinal plants have been found to be useful for diabetes management and some have been processed to isolate their active ingredients. These active ingredients are used with traditional oral anti-diabetic drugs and are not currently used alone to treat DM

Table 2. Glucose Levels of the Groups at the Pre- and Intra-Anesthesia Periods for Fed and Fasted Rats



[8]. Cherry laurel is an herb that is used against DM exclusively in rural areas in the Anatolian region.

The degree of hyperglycemia is important for the severity of diabetes symptoms [9]. Hyperglycemia, if present, is a risk factor for short and long-term cardiovascular mortality, and changes in glucose concentrations can also be harmful to neurological systems [9-11]. Therefore, glucose stability and regulation in diabetic patients is one of the predictors of successful anesthesia treatment. In critical situations, and particularly in acute conditions, good outcomes are promoted for patients by controlling glucose levels [11]. Anesthesia and surgery are critical situations in which carbohydrate metabolism is affected [12]. This may be *via* depressed insulin or glucose production during stress [12]. During anesthesia, hyperglycemia has been found to be responsible for interference in protein metabolism, which leads to changes in insulin metabolism [13]. The effects of inhalation and infusion anesthetic agents on glucose kinetics have also been previously shown [13]. In experimental studies of anesthesia involving laboratory animals such as rats and mice, a mixture of ketamine and xylazine is commonly used as the anesthetic agent [14]. Anesthetic agents such as ketamine-xylazine mixture and isoflurane are known to increase blood glucose levels in fed rodents [14]. Saha *et al.* demonstrated that the ketamine-xylazine mixture causes acute hyperglycemia (levels greater than 160 mg/dl) in fed rats [14, 15]. In their study, they also demonstrated that plasma insulin levels decreased in these rats due to ketamine usage [14]. In our study, we found that glucose levels changed significantly for fed, fasted and intra-anesthesia periods of the rats. Glibenclamide and Extract 300 groups had similar values but Extract 600 had higher difference, which meant more irregularity. The reason for irregularity in Extract 600 group has to be searched although the dose for treatment of DM was higher in this group.

This study reveals the anti-diabetic activity of cherry laurel. Carbohydrate metabolism can be affected by many variables; therefore a simple model was used in this study. The influence of environmental factors, such as handling stress, on all aspects of the metabolic pathway should be investigated to better understand the chemo-protective effect of cherry laurel [16]. For example, ketamine is known to have an effect on plasma insulin levels. Hormones such as glucagon, catecholamines, adrenocorticotrophic hormone, growth hormone and cortisol that are released under different levels of stress are known to act directly or indirectly on glucose metabolism [16]. Our study does not evaluate the histopathological details of the rat tissues fespecially pancreatic effects and also does not evaluate molecular basis of the extract. These are the weakness of the study. Therefore, this study is not a conclusive study for the anti-diabetic effect of cherry laurel. Meanwhile, it impressed that the results of this preliminary study provide justification for further, more extensive, studies on the mode of action and potential of cherry laurel as an anti-diabetic drug.

CONCLUSION

The use of herbal medicine for the treatment of various disorders has a long and extensive history. More than half of the world's population relies on traditional medicine for their therapeutic needs. Most traditional therapies involve the use of herbal extracts. In this report, we show that the herbal extract of cherry laurel has a superior anti-diabetic activity to glibenclamide. We also demonstrated the regulatory effect of cherry laurel on glucose metabolism in anesthetized rats. We postulate that cherry laurel promotes pancreatic secretion of insulin from the intact β-cells of islets, since increased levels of insulin were observed in diabetic rats. However, alternative, extra-pancreatic mechanisms such as decreased glycogenolysis, enhanced glycogenesis by the liver and the enhanced transport of blood glucose cannot be ruled out, and should be evaluated in further studies. Studies to investigate the potential antioxidant activity of cherry laurel extract are also needed. Cherry laurel appears to be an exciting anti-diabetic drug candidate, and further studies to establish the active compounds and their toxicological effects should be investigated.

CONFLICT OF INTERESTS

The author(s) declare that they have no competing interests. We all seek for a new molecule for the more effective anti-diabetic drug and we are not parts of drug industry companies.

ACKNOWLEDGEMENTS

This study was sponsored by Scientific Research Committee (B.A.P.) of Gaziosmanpasa University, Tokat, Turkey.

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Received: October 05, 2011 Revised: January 03, 2012 Accepted: February 09, 2012