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Prevention of glucose toxicity after cornelian cherry and bee bread treatment in spontaneous animal model of *diabetes*

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Abstract

Diabetes mellitus type 2 is a complex metabolic disease characterized by persistent hyperglycaemia. And it is chronic glucose toxicity that influences the development of other critical symptoms of *diabetes mellitus*. To prevent the occurrence and subsequent treatment of *diabetes*, new alternative sources are being sought. In our study, we focused on the effect of bee bread and cornelian cherry fruit (*Cornus mas* L.) administered jointly in a homogenized dose (500 mg.kg⁻¹ each) by gastric tube on the onset and development of *diabetes mellitus*, on the alleviation of symptoms of glucose toxicity and insulin resistance. We found that regular consumption of these substances resulted in improved glycaemia and had a preventive effect on glucose toxicity in young rats suffering from DM2T. Further studies are required.

1. Introduction

The primary and important fuel for pancreatic β -cells function is the monosaccharide glucose. To maintain its level in the normal range is the role of insulin, pancreatic hormone. There exists a homeostatic relationship between glucose and insulin activity. Nevertheless, this relationship can be disrupted when glucose remains at supraphysiologic level for extended period, which leads to the condition known as glucose toxicity (Rossetti *et al.*, 1990; Robertson *et al.*, 1994). Chronic increment in the plasma glucose concentration leads to growing impairment in insulin production and may contribute to insulin resistance (Rossetti *et al.*, 1990).

Diabetes mellitus (DM) is characterized as a chronic metabolic disease associated with a relative or absolute lack of insulin, resulting in hyperglycaemia. Many complications arise from chronic hyperglycaemia such as nephropathy, neuropathy, and retinopathy what can leads also to risk of cardiovascular disease (Danaei *et al.*, 2011, Simkova and Capcarova, 2024a, b). The most common types of DM are DM type 1 (DMT1) and DM type 2 (DMT2). DMT1 is thought to be precipitated by an immune-associated or maybe directly immune-mediated destruction of insulin-secreting pancreatic β -cells (Todd, 2010). DMT2 is related to insulin resistance and insufficiency of adequate compensation by the β -cells which lead to a relative insulin deficiency (Solomon *et al.*, 2008). In T2DM overweight or obesity contribute to insulin resistance through some pathways, involves an imbalance in the concentrations of hormones (increased leptin and glucagon, reduced adiponectin), increased

concentrations of cytokines (tumour necrosis factor α , interleukin 6), suppressors of cytokine signalling, other inflammatory signals, and possibly retinol-binding protein (Wellen and Hotamisligil, 2005).

Animal models of *diabetes* play an important role in the understanding of pathogenesis (Arndt *et al.*, 2013, Capcarova *et al.*, 2018). Research on *diabetes* in humans is not possible, as provocation of DM is strictly impermissible. Hence, animal models of DM are greatly useful and advantageous in biomedical research. It presents a new insight into human DM, new methods of treatment (Srinivasan and Ramarao, 2007) and the possibility of new therapeutic agents (Chen and Wang, 2005). Bee products have been used for many years in the treatment of various ailments (Capcarova *et al.*, 2020). Bee bread is fermented mixture of plant pollen, bee saliva and honey and is intended as the main feed for bee larvae (Markiewicz-Zukowska *et al.*, 2013). It is a very good source of bioactive compounds with antioxidant and antimicrobial properties (Ivanisova *et al.*, 2015). The cornelian cherry (*Cornus mas* L.) is the tree, frequently in the past in Slovak Republic. Over time it was forgotten and nowadays the scientific community has become interested in it because of its beneficial effects, e.g. also on the nervous system (Capcarova *et al.*, 2019). Its relative plant grown in Japan (*Cornus officinalis*) has been effective in DM therapy in diabetic rats due to its hypoglycaemic effect (Yokozawa *et al.*, 2008).

Relevant information on the synergistic effect of bee bread and cornelian cherry does not exist in the literature. Previously we observed a positive effect of bee bread and cornelian cherry

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applied alone to ZDF rats. In this work, we decided to investigate their joint effect. In this study we administered bee bread in the dose of 500 mg.kg⁻¹ and cornelian cherry in the dose of 500 mg.kg⁻¹ as a common mix homogenised in drinking water and administered via a gastric probe directly into the stomach of rats. We investigated their preventive effect on reducing glucose toxicity and related DM symptoms such as water intake, live weight, insulin production and insulin resistance.

2. Materials and Methods

2.1 Animals

Zucker diabetic fatty (ZDF) rats (a fatty *fa/fa* mutation (-/-); n=20) and their healthy lean controls (lean, non-diabetic, +/+ or +/-, not display expression of *fa* phenotype, n=10) of the same strain in the age of 3 months (12 weeks of age) were involved in the experiment. The male animals were purchased from Breeding Facility of the Institute of Experimental Pharmacology and Toxicology (Dobra Voda, Slovak Republic, SK CH 24016). All animals were housed in number of two rats per plastic cage (80 cm²) and under specific pathogen free conditions at 23±1°C and 55±10% relative humidity with a 12 h light-dark cycle. Rats were provided with water and diet on *ad libitum* base.

2.2 Experimental design

Rats were divided into three groups (n=10 each) as follows: lean rats (C) fed by KKZ-P/M (complete feed mixture for rats and mouse, reg.no 6147, Dobra Voda, Slovak Republic, 10 MJ/kg), diabetic rats fed by KKZ-P/M (E1, 10 MJ/kg) and diabetic rats administered bee bread and cornelian cherry each in dose 500 mg.kg⁻¹. The initial body weight did not differ between rats within the same genotype (E1, E2). The experiment lasted 4 months. Water intake and body weight were monitored once per week.

2.3 Glucose analysis

After overnight fasting rats were observed for blood glucose level by a Glucose Monitoring System (Easytouch GCHb, Ingbert/Hassel, Germany) using test stripes (Easytouch GCHb, Ingbert/Hassel, Germany) once per week. One drop of blood was collected from the tail vein in the morning between 7:00 to 9:00 a.m. After glucose measurement the rats were given the feed. *Diabetes* was defined as a blood glucose level equal to or higher than 15 mmol. l⁻¹. At the end of the experiment fasting whole blood samples were taken from the heart after deep anaesthesia. Whole blood was processed immediately and insulin content was determined.

2.4 Insulin analysis

At the end of the experiment, the animals were anesthetized via intraperitoneal injection with chloral hydrate (40 mg/100 g body weight). Blood samples were collected into EDTA-treated tubes. ELISA commercial kit (Biotech, Bratislava, Slovak Republic) was used to measure the serum content of insulin according to the instruction of the manufacturer.

2.5 HOMA-IR determination

Values of fasting plasma insulin and serum glucose were used to calculate HOMA-IR index, as mathematical model that describes interactions between fasting serum insulin and blood glucose concentration.

2.6 Statistical analysis

Data are expressed as mean ± SD (standard deviation). One-way ANOVA test was realized to calculate basic statistical characteristic and to determine significant differences. Statistical software SAS Release 9.1 (SAS Institute Inc. Cary, USA, 2002-2003) was used. Differences were compared for statistical significance at the level $P < 0.05$.

3. Results

3.1 Effect of cornelian cherry and bee bread on body weight

The body weights in control diabetic group as well as in experimental group of animals were significantly higher ($p < 0.05$) than those measured in lean animals (Fig. 1). The differences between control and experimental animals remained insignificant ($P > 0.05$) during whole experimental period. Although the weight of the animals in the control group after the 6th week of the experiment was visibly lower, although not significantly ($P > 0.05$). Animals in the control group began to lose weight that week and this trend continued until the end of the experiment. As for the treated experimental animals, although they showed obesity and hyperphagia, their body weight increased gradually like that of lean animals.

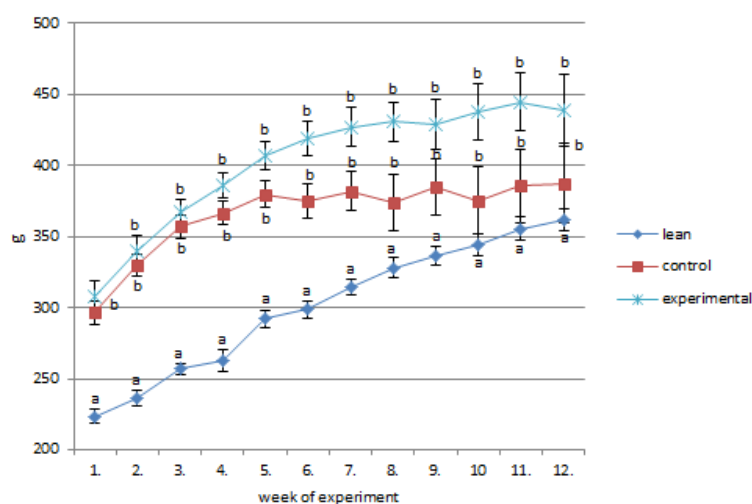


Figure 1. Effect of cornelian cherry and bee bread on body weight of ZDF rats; lean-control non-diabetic animals receiving water, control – untreated diabetic animals receiving water, experimental – diabetic animals with cornelian cherry and bee bread, body weight was monitored once per week, values are mean ± SEM, a-b in particular week means significant difference ($p < 0.05$).

3.2 Effect of cornelian cherry and bee bread on water intake

The water intake was during the whole experimental intervention significantly lower ($P < 0.05$) in lean group when compared to the control and experimental group (Fig. 2). When the control group was compared with the experimental group, we observed a significant decrease in water intake in treated experimental animals ($P < 0.05$) in the 4th and 5th week of the experiment. Water intake in the other weeks did not differ between the two groups ($P > 0.05$), although in all observed weeks of the experiment water intake was always lower in the experimental group.

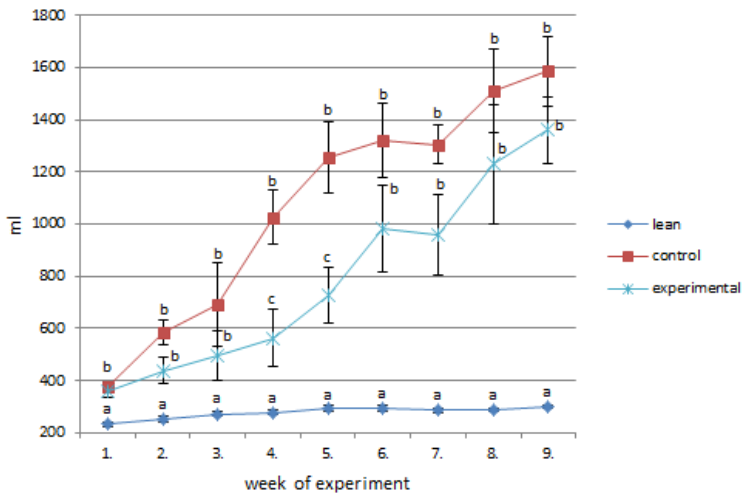


Figure 2. Effect of cornelian cherry and bee bread on water intake of ZDF rats; lean-control non-diabetic animals receiving water, control – untreated diabetic animals receiving water, experimental – diabetic animals with cornelian cherry and bee bread, water intake was monitored once per week, values are mean $\pm$ SEM, a-b, or a-c, or b-c in particular week means significant difference ($p < 0.05$).

3.3 Effect of cornelian cherry and bee bread on glycaemia

The blood glucose concentrations were well-balanced and in similar level during the whole experiment (Fig. 3) and were significantly lower ($P < 0.05$) when compared to the control and experimental group. Untreated animals from the control group showed normal glycaemia at the beginning of the experiment (1st collection of blood). Subsequently, the glucose concentration increased until the rats reached hyperglycemia in the 2nd collection or 4 weeks of the experiments (pre-diabetes), and in the 3rd collection (6 weeks of the experiment) there was an onset of diabetes in this group. The application of cornelian cherry and bee bread lowered glycaemia in all blood collection (except the first blood collection) against the control, significantly ($P < 0.05$) in 3rd blood collection (6 weeks of the experiment). The onset of DM in the treated group was in 4th blood collection.

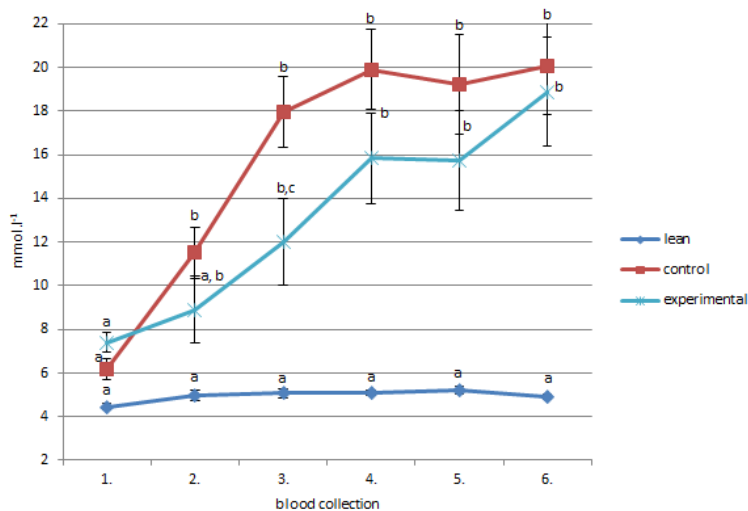


Figure 3. Effect of cornelian cherry and bee bread on glycaemia of ZDF rats; lean-control non-diabetic animals receiving water, control – untreated diabetic animals receiving water, experimental – diabetic animals with cornelian cherry and bee bread, glucose concentration was monitored once per two

weeks, values are mean $\pm$ SEM, a-b, or a-c, or b-c in particular week means significant difference ($p < 0.05$).

3.4 Effect of cornelian cherry and bee bread on insulin level

The highest level of insulin was in the lean group (Fig. 4). Significantly lower ($P < 0.05$) value was found in the control group when compared to the lean group. Treatment with cornelian cherry and bee bread increased insulin level to a level similar to the lean group, as we did not observe statistical differences ($P > 0.05$) between the average results in the two groups.

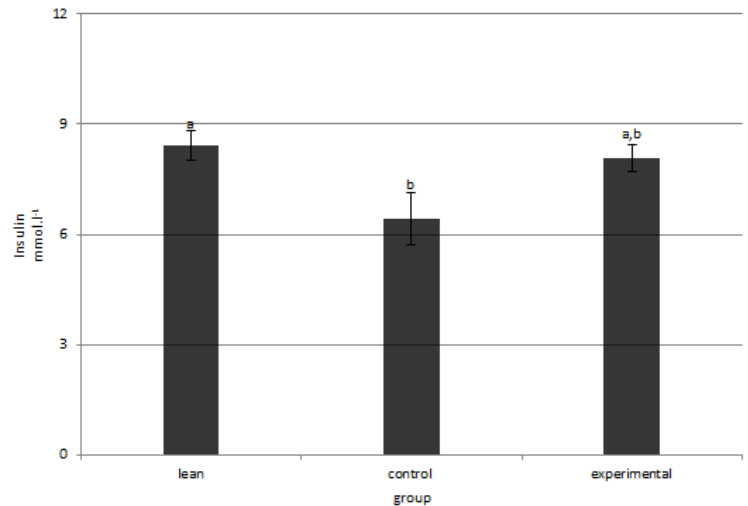


Figure 4. Effect of cornelian cherry and bee bread on insulin level; lean-control non-diabetic animals receiving water, control – untreated diabetic animals receiving water, experimental – diabetic animals with cornelian cherry and bee bread, values are mean $\pm$ SEM, a-b means significant difference ($p < 0.05$).

Effect of cornelian cherry and bee bread on HOMA-IR level

HOMA-IR was significantly higher ($P < 0.05$) in both diabetic groups (control and experimental) compared to the lean group (Fig. 5). When compared the control and experimental group the significantly lower value ($P < 0.05$) was observed in treated group.

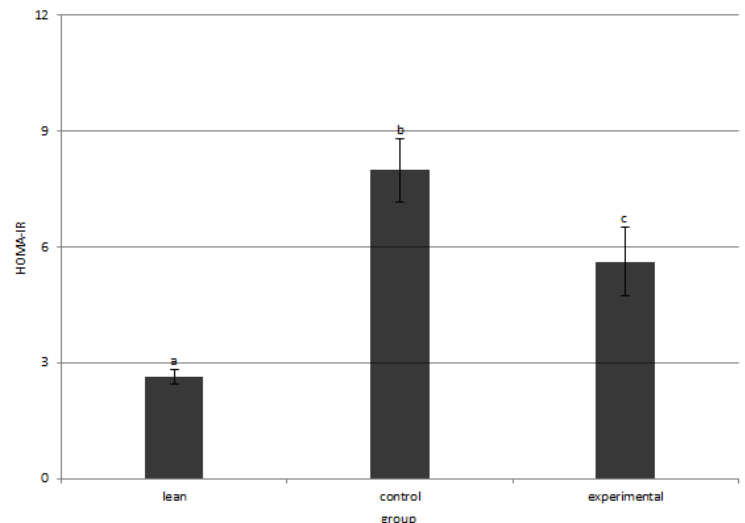


Figure 5. Effect of cornelian cherry and bee bread on HOMA-IR; lean-control non-diabetic animals receiving water, control – untreated diabetic animals receiving water, experimental – diabetic animals with cornelian cherry and bee bread, values are mean $\pm$ SEM, a-b, a-c, and b-c means significant difference ($p < 0.05$).

4. Discussion

The paper deals with the possible therapeutic effect of cornelian cherry pulp and a special bee product - bee bread - on the prevention of glucose toxicity and other related disorders associated with *diabetes mellitus*. This is based on our previous studies in which we administered bee bread using a gastric probe to rats from the ZDF line at a dose of 700 mg.kg⁻¹ (Capcarova *et al.*, 2020) and cornelian cherry pulp in the dose of 500 and 1000 mg.kg⁻¹ (Capcarova *et al.*, 2019). Both substances were given daily for 4 months what resulted in improved glycaemia and restriction in water consumption. In this study, we investigated their joint action and observed the synergistic effect on symptoms associated with the pre-diabetes and onset of *diabetes*. In this paper the administration of both substances together resulted in a reduced glucose concentration compared to the control group in all experimental weeks, significantly in the sixth week of the experiment (3rd blood collection). The onset of DM was delayed by 2-3 weeks in the treatment group compared to the control group. Following the glucose reduction, a restriction in water intake was also observed after cornelian cherry and bee bread treatment. We consider reductions in both parameters (glucose, water intake) to be important outcomes as these are critical parameters and symptoms of DM. This effect may probably be due to the anthocyanins that the cornelian cherry is rich in (Soltani *et al.*, 2015). Added to this is the hypoglycaemic effect of substances present in bee bread such as vitamins and flavonoids (Capcarova *et al.*, 2020). Flavonoids can modulate glucose transport by intestinal transporters (Song *et al.*, 2002). Hypoglycaemic effect of vitamin B5 was confirmed in the study with diabetic rats by Demirci *et al.* (2014). Alloxan-induced diabetic rats showed reduction in lipid parameters after flavonoid treatment (Onuekwuzu *et al.*, 2019). Flavonoids can reduce the production of advanced glycation end-products, as glycation may result in the onset of DM complications because of toxicity of high level of glucose – hyperglycaemia (Jung *et al.*, 2012). Another possible explanation of the potential prevention mechanism of glucose toxicity after flavonoids present in cornelian cherry and bee bread is that they exhibit α -glucosidase inhibitory activity. This makes them a potential source of antidiabetic compounds to control postprandial hyperglycaemia (Choudhury *et al.*, 2018). In our study untreated control animals intake huge amount of water, significantly higher than that of the treated experimental group. Some substances in cornelian cherry such as anthocyanins (e.g. cyanidin-3-glucoside or delphinidin-3-glucoside) were proven to stimulate insulin secretion from rodent pancreatic β -cells (Jayaprakasaam *et al.*, 2005). In our study following the application of bee bread and cornelian cherry after, there was an increase in insulin production to the level of the lean group, as the differences between lean and experimental group were not significant, which we consider as extremely positive result. In contrast, the difference between insulin production in the lean group and the untreated group was significant. The highest insulin production was found in the lean animals. The calculation of HOMA-IR can be a potentially effective tool in determination, evaluation, onset and progress of DM2T (Capcarova *et al.*, 2020). The HOMA-IR parameter is related to insulin production. The values <2.5 are reported as normal values (Gutch *et al.*, 2015). In our work the HOMA-IR significantly the highest in the untreated control group when compared to the lean and experimental rats. It is the reduced insulin production in the control group that corresponds with the HOMA-IR results, indicating that insulin resistance has developed more in the untreated group. Conversely, administration of the cornelian cherry and bee bread led to a reduction in insulin resistance in

rats, which is important in the treatment of DM. The estimate of insulin resistance is important due to its role in the pathophysiology of DM2T (Choi and Kim, 2010).

In this paper the body weight of rats increased throughout the experiment. We observed weight loss in the untreated group in comparison to the experimental and lean animals, mainly from 7th week of the experiment. Animal weight loss may just be a sign of advanced DM because of insufficient amount of insulin. The body of animals starts to burn fat and muscle to replace the energy from glucose. In a study by Dzydzan *et al.* (2019), oral application of cornelian cherry fruit led to a reduction in body weight loss in diabetic animals. El-Seedi *et al.* (2024) confirmed anti-obesity impact of bee bread in treatment of DM.

5. Conclusion

In conclusion, the regular consumption of cornelian cherry and bee bread improved glycaemia and had a preventive effect on glucose toxicity in young rats suffering from DM2T. Also decrease in water intake was observed after treatment. Rats from experimental treated group showed lower insulin resistance, balanced weight gain and decrease in water intake, thus there was an improvement in the overall health status of the animals and a refinement of DM symptoms. However, it should be noted that the intake of these applied substances must be carried out in the period before the onset of DM, i.e. in young individuals. Further studies are required.

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Declaration of interest

The author report no conflicts of interest. The author alone are responsible for the content and writing of the paper.

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