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Randomised, double blind, cross-over, placebo and active controlled human pharmacodynamic study on the influence of silver fir wood extract (Belinal) on post-prandial glycemic response

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The aim of this study was to test the extract from silver fir wood (Belinal) on the reduction of the blood glucose concentrations after consumption of a standard meal. 31 healthy participants consumed 100 g of white bread 4 times (with 1 week washout period, consequently) concomitantly with a capsule of Belinal, capsule of chestnut wood extract, placebo or acarbose (active control). Glucose and insulin in the blood were measured before and after the meal. The area under the curve of glucose concentration in blood after the meal was 35 % lower when Belinal was added compared with the placebo group ($p = 0.019$). Acarbose lowered the area for 43 % ($p = 0.002$). By this, we proved that the effect of Belinal might be beneficial for prevention of diabetes. This is the first study that provides a scientific rationale for use of silver fir wood extract as food supplement for reduction of health risks connected to type 2 diabetes mellitus.

1. Introduction

High concentration of post-prandial glucose in blood is a significant risk factor for the development of diabetes, cardiovascular disease and some types of cancer (Augustin et al. 2003; Dickinson et al. 2004; Gerich 2003; Hodge et al. 2004; Silvera et al. 2004). On the other hand, food which produces low post-prandial blood glucose responses reduce the risk of developing these diseases, and improve insulin sensitivity (Brand-Miller 2003; Frost et al. 1998; Opperman et al. 2004; Rizkalla et al. 2002; Roberts et al. 2003). Studies in humans and animals also show, that low glycemic index (GI) diets reduce body fat deposition (Brand-Miller et al. 2002; Ludwig 2003; Pawlak et al. 2004). Diabetes mellitus type 2 comprises a group of metabolic disorders characterized by hyperglycemia and abnormal carbohydrate metabolism. It is associated with several acute and long-term complications: ophthalmologic, renal, neurologic, gastrointestinal, genitourinary and cardiovascular diseases (ADA 2015; Nathan et al. 2009; Li et al. 2013; Lin et al. 2010; Wang et al. 2013). There is an urgent need for the treatment of diabetes owning to the huge complications induced by diabetes and the fact that the last decade has seen a worldwide explosive increase in diabetes mellitus type 2 (Gao et al. 2013). Presently, treatment of diabetes primarily involves reduction in hyperglycaemia by various groups of synthetic medicines in addition to insulin (Geldenhuys et al. 2010; Vila-Carriles et al. 2007; Melo et al. 2006; Bharatam et al. 2005). Many studies confirmed that lifestyle modifications, including weight-reducing diets and exercise programs, are very effective in precluding or delaying Type 2 diabetes in high risk populations with impaired glucose tolerance. Some currently-available drugs have been established as being effective in preventing diabetes in subjects with diabetes, including Metformin (Chiasson 2007), acasbore (Chiasson et al. 2002) and rosiglitazone (Bosch et. Al. 2006; Gerstein et al. 2006). However, due to adrose drug reactions, there is an increased demand for use of supplementary treatments, including functional foods and nutraceuticals (Patil et al. 2013; Patil et al. 2012; Ghosh et al. 2012; Moller 2001). It is currently believed that controlling postprandial hyperglycemia is an efficient therapeutic approach to manage diabetes and this process is generally realized by retarding two key enzymes in the digestive system linked to the adsorption of glucose (α-amylase and α-glucosidase), so the search for α-amylase and α-glucosidase inhibitors are still in the focus of research (Gao et al. 2013). Some polyphenolic compounds exert inhibitory activities on the α-amylase and/or α-glucosidase. Polyphenols are secondary compounds widely distributed in the plant kingdom. They are divided into several classes, for example phenolic acids, flavonoids, stilbenes, and lignans, which are distributed in plants and food of plant origin (Manach et al. 2004). Plant polyphenols are strong antioxidants that complement and add to the functions of antioxidant vitamins and enzymes as a defense against oxidative stress caused by excess of reactive oxygen species (ROS). Although most of the evidence of the antioxidant activity of polyphenols is based on *in vitro* studies, increasing evidence indicates they may act in ways beyond their antioxidant functions *in vivo*. With respect to cardiovascular health, polyphenols may alter lipid metabolism, inhibit low-density lipoprotein (LDL) oxidation, reduce atherosclerotic lesion formation, inhibit platelet aggregation, decrease vascular cell adhesion molecule expression, improve endothelial function and reduce blood pressure (Drevenšek et al. 2015). Polyphenols have also been shown to exert beneficial cognitive effects, to reverse specific age-related neurodegeneration and to exert a variety of anti-carcinogenic effects including an ability to induce apoptosis in tumor cells (Vauzour et al. 2010), inhibit cancer cell proliferation, prevent angiogenesis and tumor cells invasion (Mojzis et al. 2008). Epidemiological studies support favourable effects of polyphenol-rich diets in preventing and managing type 2 diabetes (Kitture et al. 2013a, b; Bhat et al. 2011; Hanhineva et al. 2010). The hypoglycemic effects of dietary polyphenolic compounds may be related to inhibition of carbohydrate digestion by inhibiting salivary and pancreatic α-amylase and α-glucosidase in the small intestinal brush border, inhibition of glucose absorption, and stimulation of insulin secretion and protection of pancreatic β-cells against glucotoxicity. Polyphenols may suppress glucose release from the liver, and improve glucose uptake in peripheral tissues by modulating intracellular signalling (Hanhineva et al. 2010). Growing evidence from *in vitro*

studies, animal models and some clinical trials suggest that they can potentially be used to control postprandial hyperglycemia in type 2 diabetes mellitus and to prevent its long-term complications (Bahadoran et al. 2013; Funke et al. 2005). One of the most intensively investigated mixtures of polyphenols that exerts, antidiabetic activity is Pycnogenol, isolated from bark of pine three (*Pinus maritima*). Pycnogenol lowered fasting and postprandial blood glucose levels in a dose dependent manner and improved endothelial functions by lowering endothelin-1 level and increasing prostacyclin and nitric oxyde (NO) concentration in blood (Liu et al. 2003, 2004). In order to find novel natural polyphenolic extract that might influence on the level of postprandial glucose, we tested a number of plant polyphenols including those found in the extract from the silver fir (Tavčar Benković et al. 2014) on their inhibitory activity against α-amylase and α-glucosidase (Roškar et al. 2016). Encouraged on the results obtained *in vitro*, we performed this human intervention study. The aim of this randomised, double blind, cross-over, placebo controlled and active controlled human pharmacodynamic study was to test if the extract from silver fir wood (Belinal) reduces the blood glucose concentrations after the consumption of a standard meal and to compare its effect with the effect of acarbose, chestnuts extracts and placebo.

2. Investigations, results and discussion

2.1. Plasma glucose and insulin concentrations

Plasma glucose concentrations increased significantly 30 min after consumption of standard meal, regardless of the test substance that was used concomitantly (Fig. 1). The concentrations remained significantly higher than baseline values by 60 min for acarbose and Belinal, but significantly lower compared to placebo and chestnut extract. After 90 min the values remained elevated for placebo and chestnut extract, but not for Belinal and acarbose. After 120 min the concentrations in all four groups did not differ to initial fasting concentrations. It can be seen, that average concentrations were lowest when the volunteers used acarbose, slightly higher with Belinal and the highest with placebo and chestnut wood extract. The differences between the blood glucose concentrations were not significantly different between four groups at any individual time point, but the area under the curve did differ significantly (see next chapter).

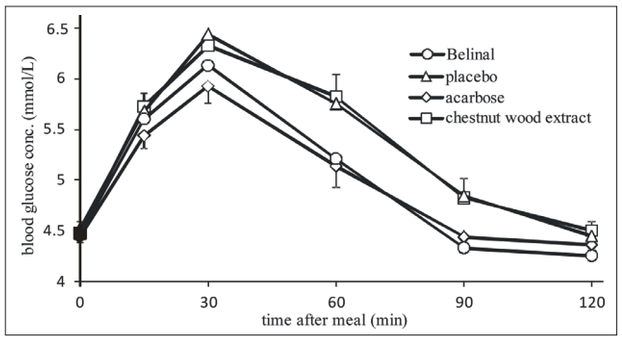

Fig. 1: The concentration of glucose in blood before (time 0) and after consumption of standard meal concomitantly with placebo, acarbose or Belinal.

It can be seen in Fig. 1 that at 15 min glucose concentration in the Belinal group was not yet lower than under placebo, but at 30 min an important difference appeared. This might be due to the lag time needed for the capsule to disintegrate and Belinal powder to dissolve in stomach fluid (the capsules did not contain any disintegrating excipents). Stronger effects of Belinal can be expected, if Belinal would be taken 15 minutes before the meal.

Plasma insulin concentrations in fasting subjects were in the normal range (8–11 μIU/mL) and were significantly elevated 60 min after the meal (Fig. 2). The elevations were highest for placebo and chestnut wood extract and lower for acarbose and Belinal. Compared to placebo, the average post prandial concentration was in the acarbose group 30 % lower (paired t-test: $p = 0.048$), in Belinal group 25 % lower ($p = 0.010$) and in chestnut wood group it was 4 % lower (non significant).

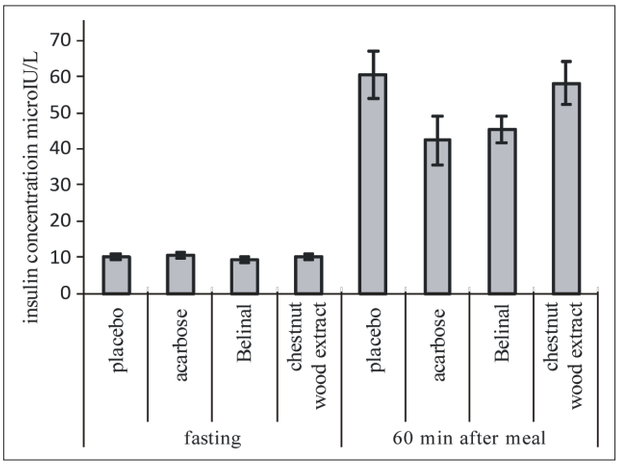

Fig. 2: Concentration of insulin in blood before and 60 min after consumption of a standard meal concomitantly with placebo, acarbose, Belinal or chestnut wood extract.

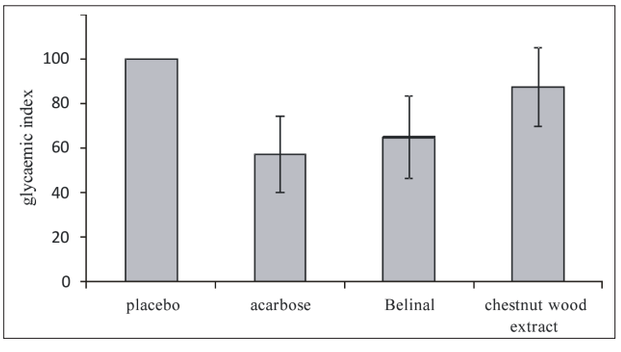

Fig. 3: Glycemic index of standard test meal ingested with placebo, acarbose, Belinal and hestnut wood extract.

2.2. Glycemic index

The glycemic index of the standard test meal ingested with Belinal was 65 % and with acarbose it was 57%. Both glycemic indices are significantly lower ($p = 0.019$ and $p = 0.002$, respectively) than the glycemic index of the standard meal with placebo, which is by definition 100 %. The glycemic indices of Belinal and acarbose did not differ significantly ($p= 0.269$). Glycemic index of chestnut wood extract was 87 % and was not significantly different from placebo.

2.3. Conclusions

A number of well-performed large epidemiologic studies demonstrate that consumption of functional foods containing bioactive polyphenols, including green tea, cocoa, and citrus fruits, are associated with dose-dependent improvement in metabolic and/or cardiovascular morbidity and mortality (Buijsse et al. 2006; Dauchet et al. 2014; Joshipura et al. 1999; Joshipura et al. 2001; Kuriyama et al. 2006; Mink et al. 2007; Peters et al. 2001; Yamada et al. 2011, Solayman et al. 2016).

The mechanisms of polyphenols and phenolic compounds in controlling blood glucose in diabetic patients include inhibition of glucose absorption, protection of pancreatic β-cell damage, improvement of insulin release and sensitivity, diminution of inflammation, modulation of carbohydrate metabolism pathway and independent signaling pathways (Patel et al. 2012; Bahadoran et al. 2013; Williamson et al. 2013).

Our research group, encouraged on the results obtained in epidemiological, animal, *in vitro* and *in vivo* studies, performed randomised, double blind, cross-over, placebo controlled and active controlled human pharmacodynamic study to test the influence of silver fir wood extract (Belinal) on the post-prandial glycemic response and to compare its effect with effect of acarbose, chestnuts extracts and placebo.

Our results showed that the addition of Belinal in a form of capsule to a standard meal reduced the glycemic index of the meal by 35 %. This means 35 % reduction of post-prandial glucose concentration in blood, therefore a reduction of risk factor for the development of many diseases including diabetes, cardiovascular disease and some types of cancer. The observed reduced pancreatic secretion of insulin with Belinal shows even further, that Belinal prevents the overload of pancreas and its possible damage. Furthermore, the reduced post-prandial blood glucose shows that the absorption of glucose is reduced or delayed from the meal accompanied by Belinal, which both could contribute to the control of body weight. However, further investigations using human longer clinical studies are required to fully establish the beneficial effects of polyphenolic compounds as supplementary treatments for

metabolic disorders associated with insulin resistance and their cardiovascular complications

before they can be used as good alternative in the management of diabetic patients.

3. Experimental

3.1. Test substances

Silver fir wood extract (Belinal) was obtained from the company Alpe Pharma (Slovenia). Belinal originates from wood from Slovene forests and it is produced by water extraction followed by spray drying, according to Roskar et al. (2016), and Drevensek et al. (2015). We filled 31 empty agar capsules with 200 mg of silver fir wood extract, 31 empty vegetarian capsules with 50 mg of acarbose, which was purchased from Sigma (Germany), 31 empty vegetarian capsules with 200 mg of chestnut wood extract and 31 empty vegetarian capsules with maltodextrin (Sigma), which was used as placebo. We numbered the capsules. The information about their content had only the principal investigator.

3.2. Study design

A total of 31 healthy volunteers (15 male, 16 female), medical students, aged 19 to 25 years completed the study. They were all from the Faculty of Medicine, University of Maribor. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (18/11/14). Informed written consent was signed by each participant before inclusion in the study. To be eligible for participation in this study, a candidate met all of the following inclusion criteria and none of the exclusion criteria. Inclusion criteria were predefined as follows: volunteers aged 19–25, both males and females, with Body Mass Index (BMI) 18.5-25, without any known disease and with normal results from oral glucose tolerance test (OGTT). Exclusion criteria were hypersensitivity to acarbose, polyphenols or any of the used excipents (maltodextrin, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, maize starch, agar), inflammatory bowel disease, chronic intestinal diseases associated with marked disorders of digestion or absorption, states which may deteriorate as a result of increased gas formation in the intestine, e.g. larger hernias, severe renal impairment, hepatic impairment, pregnancy and lactation, diabetes mellitus, impaired glucose tollerance, BMI higher than 25 or lower than 18.5, use of corticosteroids, antacids, cholestyramine, intestinal adsorbents, digestive enzymes, angiotensin-converting-enzyme inhibitors (ACE inhibitors). The study used a double-blind, randomised, cross-over design. Participants attended the laboratory on 5 separate occasions in the morning, after an overnight fast, with a wash-out period of 7 days between consecutive visits. Participants were instructed to maintain similar patterns of food intake and physical activity during the 24 h prior to each visit. At their first visit at the laboratory a venous blood sample was taken for determination of baseline plasma glucose and oral glucose tolerance test was performed to exclude volunteers with diabetes or impaired glucose tolerance. At every of the following 4 visits a venous blood sample was taken for determination of baseline plasma glucose and insulin concentrations, after which the subjects consumed 100 g of white bread containing 50 g of digestible starch combined with a capsule containing placebo (control), 200 mg of Belinal, 200 mg capsule containing chestnut extract or 50 mg of acarbose. The sequence of these 4 tests was randomised. Blood samples were taken at selected time points for determining glucose levels (0, 15, 30, 60, 90 and 120 min) and insulin levels (0, 120 min) post-prandially in order to determine the plasma glucose and insulin responses to the meal. Blood samples were sent for analysis to Department of Laboratory diagnostics, University Medical Centre Maribor, where glucose blood levels were analised and to the Department of Nuclear Medicine, University Medical Centre Maribor, where insulin blood levels were determined. The blood glucose level was measured by glucose oxidase method, the blood insulin level was determined by Radioimmunoassay (RIA).

3.3. Calculation of glycemic response and statistical analysis

The area under the curve (AUC) was calculated for each person and each test from the concentrations of glucose measured in the blood samples which were taken immediately prior to the consumption of the meal, and 15, 30, 60, 90 and 120 min after the subjects began consuming the meal, using the incremental AUC (iAUC) method (14). Glycemic index was calculated for each subject as a radio between AUC in test substance and AUC in placebo. The mean glycemic index was calculated as harmonic mean, since the ratio values for individual patients were not distributed in normal distribution.

Data shown in the tables and figures represent mean and standard error SE unless otherwise stated. An alpha level of $p < 0.05$ was taken significant.

Conflict of interest: None declared.

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