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# Mulberry leaf extract intake reduces hyperglycaemia in streptozotocin (STZ)-induced diabetic rats fed high-fat diet

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ABSTRACT

This study evaluated the antioxidant activity and anti-diabetic effect of mulberry (*Morus alba* L. *wielkolistna zolwinska*) leaf extracts in diabetic rats fed a high-fat diet. After initial 4-week high-fat diet, streptozotocin was injected in Wistar rats to induce non-obese type 2 diabetes. After confirmation of diabetes, animals were treated with mulberry dried leaves, leaf-derived ethanol or acetone extracts added to high-fat diet for 4 weeks. Mulberry ethanol extract with higher level of phenolics – chlorogenic acid and flavonol glucosides was more effective than acetone extract or dry leaves in the lowering of blood glucose, increasing insulin level and markers of antioxidant activity. The results confirm key mechanisms related to the effect of mulberry and its bioactive components on modulation of glucose metabolism through correcting hyperglycaemia, increasing insulin secretion, and improving antioxidant status in STZ-induced non-obese diabetic rat model. Antidiabetic effects exerted by mulberry leaves might depend on the extraction process.

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## 1. Introduction

Recent reports indicate that mulberry (*Morus alba* L.) leaves and leaf-derived extracts are a rich source of polyphenol antioxidants, including phenolic acids and flavonoids, such as caffeic acid, 5-caffeoylquinnic acid, kaempferol-3-O-(6-malonyl) glucoside, quercetin-3-O-(6-malonyl)-b-D-glucopyranoside, or quercetin-3-O-glucoside (Thabti, Elfalleh, Hannachi, Ferchichi, & Da Graça Camposb, 2012). Mulberry fruits and leaves extracts exhibited hypoglycaemic, hypolipidaemic, and antiatherogenic effects in certain animal models and in humans

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(Chung, Kim, Kim, & Kwon, 2013; Katsube et al., 2006; Katsube, Tsurunaga, Sugiyama, Furuno, & Yamasaki, 2009; Memon, Memon, Luthria, Bhanger, & Pitafi, 2010; Nakamura, Nakamura, & Oku, 2009; Naowaboot, Pannangpetch, Kukongviriyapan, Kongyingyoes, & Kukongviriyapan, 2009; Song et al., 2009). The leaves are a valuable, yet low-cost material that can be used in reducing the risk and treatment of type 2 diabetes, and diseases of the cardiovascular system, urinary system, nervous system (e.g., Alzheimer's disease), as well as in weight loss.

Diabetes type 2 is one of the most common health problems in most countries of the world, particularly in developed countries in Europe, North America, and Japan. The World Health Organization (WHO) predicts that by 2025 there will be about 300 million people with diabetes (Anonym, 2011). In Poland, approximately 5–9% of adult population have type 2 diabetes (Shaw, Sicree, & Zimmet, 2010).

Nutritional etiology of diabetes type 2 includes high fat diet, which often leads to energy imbalance and obesity. Dietary approaches to diabetes type 2 can be used alone especially at the onset and in mild hyperglycaemia or in combination with oral hypoglycaemic agents or insulin (Davis, Forbes, & Wylie-Rosett, 2009; Misra, Singhal, & Khurana, 2010).

Mulberry aqueous leaf extracts are already used as adjunctive therapy in the treatment of hyperglycaemia and diabetes, as well as to reduce weight (Lee et al., 2008; Zeni & Dall'Molin, 2010). However, the mechanisms by which mulberry leaves and extracts could normalize hyperglycaemia and increase insulin level or antioxidative activity are still not completely understood. Physiological effectiveness of the extract varies depending on mulberry tree variety and extraction method (Khan et al., 2013; Memon et al., 2010; Park, Lee, Lee, & Kim, 2013; Rodríguez-Sánchez, Ruiz-Aceituno, Sanz, & Soria, 2013). We have reported that extraction with organic solvents such as acetone or ethanol could yield twofold higher amounts of the bioactive components from mulberry leaves than extraction with water (Jeszka, Kobus, & Flaczyk, 2009). It has been shown that mulberry leaf ethanol extract is absorbed better than aqueous extract in the rat digestive tract (Lee, Sim, & Cheng, 2007).

To the best of our knowledge, there are no studies reporting on any bioactive compound(s) extracted or isolated from *Morus alba* L. cultivated in Poland. In addition, there is limited information on anti-diabetic properties of the mulberry extracts as a component of a high-fat diet fed to rats with type 2 diabetes. Thus, the aim of the study was to evaluate the antidiabetic potential of mulberry leaf extracts obtained using different extraction methods, as well as their antioxidant activity in STZ-induced diabetes type 2 fed high fat diet.

## 2. Materials and methods

### 2.1. Preparation of mulberry dried leaves and leaf extracts

Mulberry (*Morus alba* L. Polish variety: *wielkolistna zolwinska*) leaves were collected from the experimental plant farm (Institute of Natural Fibers and Medicinal Plants, Poznan, Poland). The leaves (50 kg) were dried in a convection dryer (Rational CCC 61/02, Germany) at 60 °C for 6 h and powdered (0.8–0.08 mm). Optimal solvents and extraction temperatures were chosen based on our previous work (Jeszka-Skowron, Flaczyk, Kobus-Cisowska, Kośmider, & Górecka, 2014). The optimal extraction conditions were (1) 65% acetone/water (v/v) at 54 °C, repeated 3 times, and (2) 65% ethanol/water (v/v) at 63 °C repeated 3 times. Combined extracts from each process were filtered using Whatmann filter paper no. 1:11 μm (Whatmann, Bedford, MA, USA) and air-dried. After solvents evaporation, the extracts were freeze-dried (Christ Alpha 1-4, LSC, Osterode am Harz, Germany).

### 2.2. Determination of DNJ, total phenolics and flavonoids, phenolic acids, flavonols content and antioxidant activity of mulberry leaf extracts

Alkaloid DNJ (1-deoxynojirimycin) was determined using Acquity UPLC TM interfaced with MS/MS Quattro micro TM API and the Acquity UPLC BEH C18 column (2.1 × 100 mm; 1.7 μm) (Waters, Milford, MA, USA) at 25 °C for 3 min. Fragmentation conditions for MS/MS were from 164 to 145.9 m/z. Glucosamine was used as an internal standard. The flow rate of the mobile phase (0.1% of formic acid in acetonitrile and methanol 70:30; v/v) was 0.3 ml/min and injection sample volume was 5 μL.

Total phenolic content was measured with Folin–Ciocalteu's reagent and gallic acid as an external standard. The results were expressed as gallic acid equivalents (GAE) g/100 g extract dry mass (DM) (Cheung, Cheung, & Ooi, 2003). Total flavonoids content was analysed using Dowd method and quercetin as an external standard (Meda, Lamien, Romito, Millogo, & Nacoulma, 2005). The results were expressed as quercetin equivalents (QUE) g/100 g extract dry mass (DM).

Chlorogenic acid, caffeic acid, gallic acid, vanillic acid, quercetin 3-(6-malonylglucoside), rutin, isoquercetrin, kaempferol 3-(6-malonylglucoside), and astragalin were determined using Agilent Infinity 1290 with Infinity Bin Pump DAD 1290 (Agilent Technology, Santa Clara, CA, USA), and the Zorbax SB C18 column (3.9 × 150 mm; 5 μm) (Agilent Technology, Santa Clara, CA, USA) in 260 nm (for hydroxybenzoic acids), 310 nm (for hydroxycinnamic acids), and 370 nm (for flavonols). The flow rate of the mobile phase (water with formic acid – pH 2.7 and acetonitrile in water 50:50; v/v) was 1.0 ml/min and injection sample volume was 10 μL.

Total antioxidant capacity was determined using 2,2′-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) as described previously (Re et al., 1999). Antioxidant activity of extracts is expressed in mM Trolox equivalent/100 g extract DM. Radical scavenging capacity against DPPH (2,2-diphenyl-1-picrylhydrazyl) was determined as described previously (Amarowicz, Pegg, & Bautista, 2000). Antioxidant activity was calculated as a percentage of $DPPH^{\bullet}$ change in absorbance and was expressed in mM Trolox equivalents/100 g extract DM. All determinations were performed in triplicate.

### 2.3. Animals

Male Wistar rats (214–301 g, 8-week-old) were purchased from the Poznan University of Medical Sciences (Poznan, Poland) and housed at the Animal Care Facility at the Poznan University of Life Sciences. The animals were kept in separate (polypropylene) cages in a temperature- and humidity-controlled

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