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Original article

Chamomile (*Matricaria recutita* L.) decoction extract inhibits *in vitro* intestinal glucose absorption and attenuates high fat diet-induced lipotoxicity and oxidative stress

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ABSTRACT

The present study aimed to investigate the inhibitory effect of chamomile decoction extract (CDE) on intestinal glucose absorption as well as its protective role against high fat diet (HFD)-induced obesity and lipotoxicity in rats. We used the Ussing chamber system to investigate the effect of CDE on intestinal transport of glucose. Male Wistar rats were fed HFD for six weeks to provoke obesity. CDE (100 mg/kg, *b. w. p.o.*) has been per orally administered to HFD fed rats. *Ex vivo*, we found that CDE significantly and dose-dependently increased intestinal absorption of glucose. *In vivo*, HFD increased the body, liver and kidney weights, while CDE treatment showed a significant protective effects. High fat diet induced also a lipid profiles disorder and a disturbances in kidney and liver function parameters. Moreover liver and kidney lipotoxicity is accompanied by an oxidative stress status characterized by increased lipoperoxidation, depletion of antioxidant enzymes activity and non-enzymatic antioxidant (-SH groups and GSH) levels as well as increased levels of free iron, hydrogen peroxide (H_2O_2) and calcium. However, treatment with CDE alleviated all the deleterious effects of HFD feed. These findings suggest that chamomile decoction extract can be used as functional beverage against obesity, hyperglycemia and hyperlipidemia.

1. Introduction

Obesity has become the first non-infectious inflammatory disease in the history of mankind. It is defined as an excessive or abnormal accumulation of adipose tissue that may impair health [1]. Intra-abdominal or visceral Obesity has a deleterious effects on several metabolic pathways, leading to the development of several pathologies such as cancer [2], respiratory abnormalities [3], neurological [4], and cardiovascular diseases [5]. Obesity is known to be associated with an oxidative stress status, defined by an excess of reactive oxygen species (ROS) relative to the antioxidant defense systems [6]. These ROS may come from mitochondrial respiratory chain and the NADPH oxidase, but obesity itself can induce oxidative stress [7]. These conditions are favorable to the development of insulin resistance and metabolic syndrome, particularly through the deregulation of adipokines and pro inflammatory cytokines [6]. Many drugs have been used for the treatment of obesity, but most of them were withdrawn from the market because of their adverse effects and their high toxicity [8]. Thus, looking for agents who possess the same pharmacological efficacy than marketed drugs, with minimal side effects deserves attention from researchers.

Matricaria recutita L. is known under the name of German chamomile. She is one of the most popular medicinal plants and can be eaten daily as herbal tea [9]. Indeed, chamomile is included in the pharmacopoeia of 26 countries worldwide [10]. Chamomile must be harvested in spring; the late harvest would reduce the quality of the active substances [11]. Phytochemical screening of chamomile flowers revealed its richness in beneficial active molecules such as phenolic compounds and terpenoids [9,12,13].

Due to its antioxidant [12,14] and anti-inflammatory [15,16] properties, chamomile extracts exhibit many beneficial health effects such as hepatoprotective [12], gastroprotective [17] and neuroprotective [18] activities. However, *Matricaria recutita* has not been investigated so far for its antiobesity effect. In this respect, we studied in this work the effect of chamomile decoction extract

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on intestinal glucose absorption and its protective effect on HFD-induced renal and hepatic lipotoxicities in rats. We also analyzed the implication of oxidative stress and some intracellular mediators in such protection.

2. Methods

2.1. Reagents

5,5-dithiobis(2-nitrobenzoic acid) (DTNB), trichloroacetic acid (TCA), acetylcholine iodide, S-butyrylcholine, butylhydroxytoluene (BHT), methanol, ether, bovine serum albumin (BSA), d-glucose and NaCl were purchased from Sigma-Aldrich Co. (Germany).

2.2. Preparation of chamomile decoction extract

Chamomile flowers were collected from the region of Beja (North-West of Tunisia) during March 2013. The plant material was later dried in an incubator at 40 °C during 72 h and powdered in an electric blender. The decoction was made with double distilled water (1/5; w/v) at 100 °C during five minutes under magnetic agitation and the homogenate was filtered through a colander (0.5 mm mesh size). Finally, the obtained extract (CDE) was stored at −80 °C until used. Chemical composition of CDE (Table 1) was determined according to Sebai et al. [19].

2.3. Effect of CDE on ex vivo intestinal glucose absorption

Male adult mice were fasted 18 h with water *ad libitum*. Animals were sacrificed by vertebral dislocation. The jejunum was removed and rinsed in cold saline solution. The mesenteric border was carefully stripped off using forceps. The intestine was then opened along the mesenteric border, and four adjacent proximal samples were mounted in Ussing chambers (exposed area, 0.30 cm2). The tissues were bathed into 3 mL of carbogen-gassed Krebs-Ringer bicarbonate (KRB) solution on each side. In the solution bathing the mucosal side of the tissue, glucose was replaced with mannitol. Both solutions were gassed with 95% O_2–5% CO_2 and kept at constant temperature of 37 ± 0.5C (pH at 7.4). In the solution were bathed the mucosal side of the tissue, various concentrations (10–2000 μg mL^{-1}) of CDE, were added 3 min before the luminal glucose (50 mmol L^{-1}) addition. Each set of experiments included a positive control of glucose-induced Isc. Results were expressed as the difference (Δ Isc) between the peak Isc after glucose challenge and the basal Isc.

2.4. High-fat diet (HFD) preparation

High-fat diet (HFD) was prepared by soaking commercial food pellets into warmed (100 °C) and liquefied abdominal fat from animal origin (sheep) during 15 min and allowed to dry at room temperature.

2.5. Animals and treatment

Healthy adult male *Wistar* rats (200–220 g body weight-15 weeks old) were purchased from the Pasteur Institute of Tunis and used in accordance with the local ethics committee of Tunis University for the use and care of animals in accordance with the NIH recommendations. They were provided with standard food (standard pellet diet- Badr Utique-TN) and water *ad libitum* and maintained in animal house at controlled temperature (22 ± 2 °C) with a 12 h light-dark cycle. Rats were divided into four groups of 10 animals each. The animals were fed with standard diet (SD) (group I and II) or high-fat diet (HFD) (group III and IV) for 6 weeks.

Groups I and III served as SD and HFD controls and had a physiological solution (NaCl, 0.9%, *p.o.*). Groups II and IV were treated with CDE (100 mg/kg, *b.w. p.o.*) for 6 weeks. Preliminary experiment indicated that 100 mg/kg *b.w* CDE was the lowest doses that give a significant protective effect. At the end of the experimental period, the animals were sacrificed, following overnight fasting. The liver and kidney were rapidly excised and homogenized in phosphate buffer saline (KH_2PO_4/K_2HPO_4, 50 mM, pH 7.4) with Potter-Elvehjem homogenizer. After centrifugation at 10.000*g* for 10 min at 4 °C, supernatant was used for the biochemical determination of protein, free iron, H_2O_2, calcium, −SH groups, GSH, MDA and antioxidant enzyme activities. Blood was also collected and plasma processed for lipid profile, urea, creatinine and transaminases determinations.

2.6. Biochemical estimations in liver and kidney tissues

SOD activity was estimated according to the method described by Misra and Fridovich [20]. CAT activity was measured using Aebi's method [21]. GPx activity was determined according to the method described by Flohé and Günzler [22]. Thiol groups (-SH) was performed according to Ellman's method [23] and GSH levels was performed according to Sedlak and Lindsay method [24]. MDA was estimated using the thiobarbituric acid test [25]. H_2O_2 was estimated using the method of Dingeon et al. [26]. Liver and kidney non haem iron was colorimetrically measured using ferrozine as described by Leardi et al. [27]. Tissues calcium was performed according to Stern and Lewis method [28]. Finally, the protein content was determined according to Hartree [29] which is a slight change of the Lowry method.

2.7. Assessment of liver and renal functions

Plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine were measured using commercially available diagnostic kits (Biomaghreb, Ariana, TN).

Table 1
Characterisation of phenolic compounds of CDE by HPLC-DAD-ESI-MS/MS.

Number	Rt (min)	λ_{max} (nm)	[M−H]−	Tentative identification
1	4.2	255	169	Gallic acid
2	7.7	259, 295	153	Protocatechuic acid
3	16.7	325	353	Chlorogenic acid
4	17.6	323	179	Cafeic acid
5	20.18	328	353	Cafeoylquinic acid
6	21.2	327	137	Salicylic acid
7	30.05	255, 369	301	Quercetin
8	32.8	321	391	Quinic acid derivative
9	33.56	267	299	Hydroxybenzoic acid-*O*-hexoside
10	34.43	275, 339	329	5,7,4′-Trihydroxy-6,3′-imethoxyflavone