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Original article

Cinnamaldehyde potentially attenuates gestational hyperglycemia in rats through modulation of PPARγ, proinflammatory cytokines and oxidative stress

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ABSTRACT

Cinnamon has a history of use for medicinal purposes and its major benefits have been linked to cinnamaldehyde. The present study aimed to investigate the hypoglycemic action of cinnamaldehyde against fatty-sucrosed diet/streptozotocin (FSD/STZ)-rat model of gestational diabetes. Female albino rats were divided into three groups. Group I fed with normal diet (ND) while group II and III were fed with FSD for eight weeks (five weeks pre-gestational and three weeks gestational). Rats of group III were administered with a daily oral dose of 20 mg/kg cinnamaldehyde one week before mating onward. At the 7th day of gestation, FSD-fed rats were injected intraperitoneally with STZ (25 mg/kg b.wt.) to induce gestational diabetes. Pre-mating treatment of cinnamaldehyde controls hyperphagia and glucose intolerance during the gestational period than in diabetic rats. It also reduced levels of fructosamine, total cholesterols, triglycerides, leptin, tumor necrosis factor-alpha (TNF-α), malondialdehyde (MDA) and nitric oxide (NO), while it significantly increased levels of high-density lipoprotein (HDL)-cholesterol, adiponectin, liver glycogen, reduced glutathione (GSH) and catalase activity at term pregnancy. In addition, cinnamaldehyde administration up-regulated the mRNA expression of peroxisome proliferated activated receptor-gamma (PPARγ) and also ameliorated the number of viable fetuses, implantation loss sites, fetal glucose and insulin levels. In conclusion, cinnamaldehyde has safe hypoglycemic action on gestational diabetes by potentiating insulin secretion and sensitivity through activating the antioxidant defense system, suppressing pro-inflammatory cytokines production, upregulating PPARγ gene expression and alleviating the reproductive performance.

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1. Introduction

Diabetes mellitus (DM) is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [1]. According to the International Diabetes Federation (IDF), 415 million people worldwide, or 8.8% of adults aged 20–79, are estimated to have diabetes. An additional 21 million cases of high blood glucose in pregnancy are estimated to contribute to the global burden of diabetes [2]. With the rapid global rise in the prevalence of DM, the incidence of the gestational diabetes mellitus (GDM) increased in the developing countries from 2.9% to 8.8% over the last twenty years [3] constituting a health threat to the upcoming generations.

GDM is defined as glucose intolerance of variable severity with onset or first recognition during pregnancy, irrespective of the glycemic status after delivery [4]. Insulin resistance and β-cell dysfunction are thought to be major determinants of its development. GDM expose the affected women to higher risk for subsequent development of type 2 diabetes (T2D) and cardiovascular diseases later in life, and their infants revealed a greater incidence of obesity and T2D in adulthood [5].

Peroxisome proliferator activated receptors (PPARs) are a family of ligand activated transcription factors belonging to the nuclear hormone receptor superfamily. PPARs regulate the expression of multiple genes involved in metabolic, anti-inflammatory, developmental processes and are involved in the maternal adaptational

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dynamics during pregnancy to serve the requirements of the growing fetus [6]. Three PPAR isotypes have been identified in mammals termed PPARα, PPARβ and PPARγ [7]. PPARα exists at the highest level in the liver and is believed to play a critical role in the regulation of fatty acids metabolism, PPARβ is ubiquitously distributed with a higher expression in the digestive tract, while PPARγ is mostly expressed in the adipose tissue, placenta and immune system. Moreover, PPARγ is a key regulator of glucose and lipid metabolism, promotes preadipocyte differentiation, stimulates the storage of fatty acids in adipocytes and enhances insulin sensitivity [8].

In general, medications preferred to be avoided during pregnancy, but for women with chronic conditions in pregnancy such as epilepsy, psychiatric disorders and diabetes mellitus, the use of medication may be required and discontinuation of treatment is not always an option. Historically, insulin has been the therapeutic agent of choice for controlling hyperglycemia in pregnant women. Difficulty in insulin administration with multiple daily injections, potential for hypoglycemia that occurs in approximately 71% of women who take insulin at some times during their pregnancy and the increase in appetite and weight makes this therapeutic option cumbersome for many pregnant patients [9]. Although the use of the synthetic oral hypoglycemic agents (SOHAs; metformin and glyburide) in pregnancy has opened new vistas for GDM management, they have dermatological and gastrointestinal adverse effects including diarrhea, flatulence, nausea and vomiting with an incidence rate 63% [10] rather than being expensive.

Medicinal plants provide valuable and safe therapeutic agents, both in modern medicine and in the traditional system. *Cinnamomum zeylanicum* (cinnamon) has a history of use for medicinal purposes as far back as in China and ancient Egypt. Non-medical reports claimed that cinnamon administration at large doses during pregnancy was implicated in triggering uterine contractions and stimulating preterm labor. Coumarin (naturally occurring constituent of cinnamon) and its derivatives may be involved in that case [11]. Cinnamon bark contains a wide range of essential oils, mainly *trans*-cinnamaldehyde. Biological activities of cinnamaldehyde (Ci) mainly include antioxidant [12] and anti-inflammatory [13] properties. In addition, Subash-Babu et al. [14] reported the antihyperglycemic effect of cinnamaldehyde in streptozotocin (STZ)-induced diabetic rats with a recommended dose of 20 mg/kg b.wt.

Although the safety evaluation of cinnamaldehyde administration during pregnancy revealed non-embryotoxic effects [15], no data are available about its role in controlling the elevated blood glucose level during pregnancy and its effect on maternal outcome and the fetal glycemic state. This study was designed to investigate the hypoglycemic action of cinnamaldehyde against FSD/STZ-rat model that might act through up-regulating PPARγ expression which targeting both TNF-α and adiponectin; vital factors affecting insulin sensitivity and blood glucose level.

2. Material and methods

2.1. Chemicals

Ethyl acetate, *n*-hexane, streptozotocin, reduced glutathione (GSH), 5,5′-dithiobis-2-nitrobenzoic acid (DTNB, Ellman's reagent), thiobarbituric acid (TBA), 1,1,3,3-tetramethoxypropane and RNA later were purchased from Sigma Chemical Co. (USA). Metaphosphoric acid and pyrogallol were purchased from Fluka analytical (Germany). All other chemicals were of analytical grade and obtained from standard commercial supplies.

2.2. Plant material and extract preparation

The bark of *Cinnamomum zeylanicum* Blume was collected from the botanical garden of the Faculty of Agriculture, Cairo University, Egypt. The samples were identified by Dr. M. Omar, Taxonomist, Botany Department, Faculty of Science, Beni-Suef University, Egypt. Voucher specimens of *Cinnamomum zeylanicum* Blume (no. BuPD 36) were deposited in Pharmacognosy Department, Faculty of Pharmacy, Beni-Suef University, Egypt by Dr. A. Ismail. Fresh bark of *Cinnamomum zeylanicum* Blume (0.5 kg) was subjected to hydro-distillation in a Clevenger-type apparatus for 4 h. The yield (v/w) of volatile oil was 0.118%; 3.1 g. According to Subash-Babu et al. [14], biologically guided the phytochemical investigation of the resulted oil led to the isolation of a bioactive compound; cinnamaldehyde.

2.3. Animals and dietary formulas

Female albino rats (*Rattus norvegicus*) weighing about 100 ± 10 g, 60 days old were obtained from the animal house of Helwan town, Cairo, Egypt. The animals were housed individually in standard polypropylene cages and maintained in an air-conditioned atmosphere, at a temperature of 25 °C with alternatively 12 h light and dark cycles for one week before the onset of the experiment to be acclimatized.

Rats had free access to water and to two dietary regimens by feeding either the normal diet (ND) or fatty-sucrosed diet (FSD).

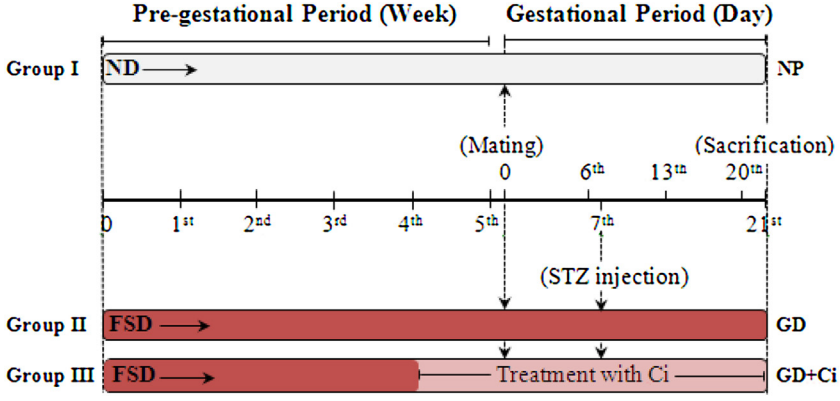

Fig. 1. Experimental design. ND, normal diet. FSD, fatty-sucrosed diet. STZ, streptozotocin. Ci, cinnamaldehyde. NP, normal pregnant. GD, gestational diabetic. GD + Ci, gestational diabetic pre-treated with cinnamaldehyde (20 mg/kg b.wt.).

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