Pharmacological Research 122 (2017) 78–89

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Cinnamaldehyde in diabetes: A review of pharmacology, pharmacokinetics and safety

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ARTICLE INFO

Article history:
Received 7 February 2017
Received in revised form 4 May 2017
Accepted 21 May 2017
Available online 27 May 2017

Keywords:
Cinnamaldehyde
Diabetes
Obesity
Pharmacology
Pharmacokinetics
Safety

ABSTRACT

Cinnamaldehyde, one of the active components derived from Cinnamon, has been used as a natural flavorant and fragrance agent in kitchen and industry. Emerging studies have been performed over the past decades to evaluate its beneficial role in management of diabetes and its complications. This review highlights recent advances of cinnamaldehyde in its glucolipid lowering effects, its pharmacokinetics, and its safety by consulting the Pubmed, China Knowledge Resource Integrated, China Science and Technology Journal, National Science and Technology Library, Wanfang Data, and the Web of Science Databases. For the inquiries, keywords such as Cinnamon, cinnamaldehyde, property, synthesis, diabetes, obesity, pharmacokinetics, and safety were used in various combinations. Accumulating evidence supports the notion that cinnamaldehyde exhibits glucolipid lowering effects in diabetic animals by increasing glucose uptake and improving insulin sensitivity in adipose and skeletal muscle tissues, improving glycogen synthesis in liver, restoring pancreatic islets dysfunction, slowing gastric emptying rates, and improving diabetic renal and brain disorders. Cinnamaldehyde exerts these effects through its action on multiple signaling pathways, including PPARs, AMPK, PI3K/IRS-1, RBP4-GLUT4, and ERK/JNK/p38MAPK, TRPA1-ghrelin and Nrf2 pathways. In addition, cinnamaldehyde seems to regulate the activities of PTP1B and α-amylase. Furthermore, cinnamaldehyde has the potential of metalizing into cinnamyl alcohol and methyl cinnamate and cinnamic acid in the body. Finally, there is a potential toxicity concern about this compound. In summary, cinnamaldehyde supplementation is shown to improve glucose and lipid homeostasis in diabetic animals, which may provide a new option for diabetic intervention. To this end, further scientific evidences are required from clinical trials on its glucose regulating effects and safety.

Abbreviations: Ach, acetylcholine; Acsl4, acyl-CoA synthetase 4; AUC_{0-t}, area under the plasma concentration-time curve from zero (0) hours to time (t); AMPK, 5′-adenosine monophosphate-activated protein kinase; BAT, brown adipose tissue; BDNF, brain-derived neurotrophic factor; BMP4, bone morphogenetic protein 4; CART, cocaine and amphetamine-related transcript; CCK, cholecystokinin; CEBP-α, CCAAT/enhancer-binding protein-α; Cmax, maximum plasma concentration; COX-2, cyclooxygenase-2; Cpt1a, carnitine palmitoyltransferase 1A; ERK/JNK/p38MAPK, extracellular signal-regulated kinase/c-Jun NH2-terminal kinase/p38 mitogen-activated protein kinases; FOXP2, forkhead box protein 2; G3P, glycerol-3-phosphate; GLUT, glucose transporter; GC–MS, gas chromatography–mass spectrometry; HDL, high density lipoprotein-cholesterol; HFD, high fat diet; HFHS, High fat and high sucrose; HSL, hormone-sensitive lipase; IL-6, interleukin-6; IR, insulin receptor; IRS-1, insulin receptor substrate-1; JNK, c-Jun NH2-terminal kinase; KCl, potassium chloride; MCP-1, monocyte chemotactic protein 1; MEF2, myocyte enhancer factors 2; MGL, monoglyceride lipase; NO, nitric oxide; NQO1, NAD(P)Hquinone oxidoreductase 1; Nrf2, nuclear factor erythroid-2 related factor 2; PEPCK, phosphoenol pyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PI3K, phosphatidylinositol-3-kinase; PK, pyruvate kinase; PNPLA2, patatin phospholipase domain containing 2; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PRDM16, PR domain containing 16; PTP1B, protein tyrosine phosphatase 1B; RBP4, retinol binding protein 4; SREBP1, sterol regulatory element-binding protein 1; STZ, streptozotocin; SME-cinnamaldehyde, submicrometer emulsions of cinnamaldehyde; $T_{1/2}$, the time taken a drug to clear from the highest concentration to half this level. TGtriglyceride; TGF-β, transforming growth factor-β; Tmax, time at maximum plasma concentration; TNF-α, tumor necrosis factor-α; TRPA1, transient receptor potential-ankyrin receptor 1; UCN, urocortin; UCP1, uncoupling protein 1; WAT, white adipose tissue.

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http://dx.doi.org/10.1016/j.phrs.2017.05.019
1043-6618/

Contents

1. Introduction

Cinnamaldehyde, an old flavourant derived from *Cinnamon* trees and other species of the genus *Cinnamomum* [1], has now attracted rising interests for its ability of preventing the development of diabetes and its complications [2,3]. As a yellow and viscous liquid, cinnamaldehyde (Fig. 1) constitutes 98% of essential oil of Cinnamon bark, and was first isolated by Dumas and Péligot [4] and then synthesized in the laboratory by the Italian chemist, Luigi Chiozza (1828–1889) in 1854 [5]. In 2007, Subash et al. firstly reported a hypoglycemic and hypolipidemic effect of cinnamaldehyde on streptozotocin (STZ)-induced male diabetic Wistar rats [6]. Cinnamaldehyde has been since extensively studied in animal models of diabetes and obesity. Here, we review recent progress of cinnamaldehyde with regarding to its activities in management of diabetes and its complications, its pharmacokinetics, and safety by consulting the Pubmed (www.pubmed.com), Chinese National Knowledge Infrastructure (www.cnki.net), National Science and Technology Library (http://www.nstl.gov.cn/), China Science and Technology Journal (http://en.cqvip.com/cstj.html), Wanfang Data (http://www.wanfangdata.com.cn/) and web of science (www.isiknowledge.com) databases.

2. The pharmacological activities of cinnamaldehyde in management of diabetes

2.1. Effect of cinnamaldehyde on glycaemia in animal models of diabetes

The hypoglycemic and hypolipidemic effects of cinnamaldehyde have been extensively evaluated in animal experiments. We summarize all the the available publications related to the applications of cinnamaldehyde in diabetic rodent models by October 2016 as shown in Table 1. Of these 13 experimental studies, male rats and mice are the most often used rodents to assess glucolipid lowering effects of cinnamaldehyde, in which diabetes models are often induced by high fat diet (HFD) plus STZ. It is demonstrated that oral administration of cinnamaldehyde ranging from 20 mg/kg·body weight (BW) to 40 mg/kg·BW per day for a duration lasting from 21 to 60 days resulted in a significant improvement in the levels of blood glucose and glycosylated hemoglobin as well as insulin sensitivity in STZ-induced diabetic rats [7–10]. And 20 mg/kg·BW is assumed to be the effective dose for preventing the development of diabetes in rats.

Further, cinnamaldehyde treatment for 4 weeks increases plasma insulin levels and liver glycogen content, as well as decreases triglyceride (TG) and low density lipoprotein-cholesterol levels in STZ and/or HFD insulted male Wistar rats[11,12]. Furthermore, Camacho et al. found that administration with cinnamaldehyde for 5 weeks to HFD fed C57BL/6J mice significantly led to a reduction in body fat mass gain. However, they claimed that cinnamaldehyde treatment did not alter plasma fasting insulin levels and feed consumption [13]. The reason for the inconsistence regarding insulin regulation could be attributed to that genetic backgrounds of C57BL/6J mice are altered in some production facilities [14,15]. The different substrains of mice may exhibit significant differences in phenotypes [16–18]. In addition, cinnamaldehyde may exhibit glucose lowering effect through improving insulin sensitivity in the periphery in Camacho's study [13].

Moreover, Cinnamon oil, which contains more than 98% cinnamaldehyde, has also been demonstrated to reduce the fasting blood glucose and total cholesterol as well as to elevate high density lipoprotein-cholesterol (HDL) in a dose-dependent manner (5–20 mg/kg) in response to alloxan challenge [19]. The similar results are also obtained in using Cinnamon oil (25, 50 and 100 mg/kg) to treat KK-Ay mice for 35 days [20]. In this study, the authors also found that the administration of Cinnamon oil decreased plasma C-peptide and improved glucose tolerance and insulin sensitivity [20]. Thus, it is reasonable to assume that cinnamaldehyde is one of main active components in Cinnamon oil regarding blood glucose regulating.

However, Hafizur et al. reported the contrasting results using STZ (90 mg/kg) insulted 2-day-old Wistar rat pups [21]. In this study, they did not found acute effects of blood glucose lowering and glucose tolerance after single administration of cinnamaldehyde (10 mg/kg) to 3-month-old diabetic rats [21]. And also cinnamaldehyde (50–200 μM) does not promote insulin secretory activity in primary islets [21]. The reason for this discrepancy may be attributed to that the dose of cinnamaldehyde administered, treatment duration and the different culture conditions [22]. One dose of cinnamaldehyde is insufficient for attaining glucose-lowering effect in diabetic rats. In addition, as mentioned above,