





Zingerone attenuates diabetic nephropathy through inhibition of nicotinamide adenine dinucleotide phosphate oxidase 4

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<https://doi.org/10.1016/j.biopha.2018.01.051> 

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Abstract

Diabetes affects a large proportion of population wide across the world and kidney is a main target organ of diabetic complications. Zingerone is a stable active component derived from dry ginger rhizome. We investigated the effect of zingerone on diabetic nephropathy and explored the possible mechanisms. We showed that zingerone decreased the levels of serum insulin, C-peptide and glycosylated hemoglobin A1c. The levels of blood urea nitrogen (BUN), serum creatinine, urinary albumin content and albumin/creatinine ratio (ACR) were reduced by zingerone. Moreover, zingerone attenuated the pathological injuries of kidneys, reduced the surface area of Bowman's capsule, Bowman's space, glomerular tuft, and decreased the expression of collagen IV and fibronectin in kidneys in db/db mice. The high levels of triglyceride and cholesterol, and high expression of TNF α and IL-6 were decreased by zingerone. Furthermore, zingerone decreased the level of MDA and increased the content of glutathione (GSH). NADPH oxidase 4 (NOX4) expression was significantly increased in kidneys of db/db mice and in HK-2 cells after exposure to high glucose. Zingerone significantly decreased the expression of NOX4 in vivo and in vitro. Upregulation of NOX4 significantly inhibited zingerone-induced protective effects against the cytotoxicity of high glucose. Downregulation of NOX4 was responsible for zingerone-exhibited pharmacological activities and reduction of diabetic nephropathy. Overall, zingerone is a promising therapeutic treatment to attenuate diabetic nephropathy.

Introduction

Diabetes affects a large proportion of population wide across the world [1,2]. The kidney has been believed to be a main target organ of complications of diabetes [3]. Approximately, 40 percent of patients suffer from diabetes may develop diabetic nephropathy, which is a major cause of end-stage renal disease [4] and can result in disability and mortality of diabetic patients [5]. To date, the molecular mechanisms underlying diabetic nephropathy are still not completely understood and the therapy is limited [6]. Diabetic nephropathy is characterized by increase of lipid profile,

inflammation, oxidative stress, accumulation of extracellular matrix (ECM) proteins and an irreversible decline in renal function [7]. Therapeutic strategies are designed to target hyperglycemia, hyperlipidemia, oxidative stress, inflammatory cytokines as well as genetic disposition [8]. The most common way is to decrease blood glucose levels and lower hypertension through blockage of the renin-angiotensin system [9,10]. However, the efficiency of these approaches is not satisfied [11]. Therefore, new alternative treatments are urgently needed to control the progression of diabetic nephropathy.

The herbal plant *Zingiber officinale*, commonly known as ginger, is consumed worldwide as a natural dietary spice and flavoring agent [12]. Zingerone [4-(4-hydroxy-3-methoxyphenyl) butan-2-one] is a stable active component derived from dry ginger rhizome (Fig. 1A) [13]. It has been reported that zingerone exhibit various pharmacological activities such as anti-inflammatory, anti-apoptotic, antioxidant, anti-cancer, lipolytic, and radioprotective effects [[14], [15], [16], [17], [18]]. Zingerone ameliorates lipopolysaccharide-induced acute kidney injury by inhibiting Toll-like receptor 4 signaling pathway [19]. Zingerone also exhibits nephro-protective effect against CCl₄-induced renal toxicity in Swiss albino mice [20]. The findings suggest that zingerone possesses a potent nephro-protective effect. However, whether zingerone possesses biological effects on kidney function under diabetic condition is not known.

The present study aimed to assess the possible effect of zingerone on diabetic nephropathy in db/db mice and to explore the possible mechanisms. We found that zingerone could attenuate the progression of diabetic nephropathy as reflected by amelioration of renal structural and functional injuries. Zingerone exhibited anti-inflammatory, hypolipidemic, anti-oxidative activities in db/db mice. Downregulation of NADPH oxidase 4 (NOX4) was involved in the protective effect of zingerone against diabetic nephropathy.

Section snippets

Reagents

Zingerone was obtained from Sigma-Aldrich Inc. (Saint Louis, MO, USA). 5-(and-6)-carboxy-2', 7'-dichlorodihydrofluorescein diacetate (DCFDA) was obtained from Invitrogen. NOX4 antibody was purchased from Cell Signaling Biotechnology (CST, USA). β -actin antibody was obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Secondary antibodies were obtained from Thermofisher Scientific Biotechnology....

Animals and treatment

The animal procedures and experimental protocols have been approved by the Ethics Committee...

Zingerone attenuates glucose metabolic abnormality in db/db mice

Firstly, the effect of zingerone on glucose metabolism in db/db mice was examined. We found that zingerone significantly reduced the body weight of db/db mice, with no significant effect on the body weight of WT mice (Fig. 1B). Although fasting blood glucose level was not significantly altered by zingerone, level of HbA1c in db/db mice was notably decreased (Fig. 1C and D). The high levels of serum insulin and C-peptide were decreased by zingerone (Fig. 1E and F). We did not observed marked...

Discussion

Considering the fact that zingerone exhibits various pharmacological and biological activities, the present study was performed to evaluate the possible effect of zingerone on diabetic nephropathy. Although zingerone had no significant effect on blood glucose and glucagon level, it significantly decreased the levels of HbA1c, insulin, and C-peptide in db/db mice. The results indicated that the effect of zingerone on renal function was not associated with changes of glucose level, but may be...

Conflict of interest

The authors declare that there are none conflict of interest....

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2022, Phytomedicine Plus

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...Chinese herbal medicines, Tong Xinluo (TXL) (Zhang et al., 2014a), Huangkui capsule (Han et al., 2019), and herbal mixture, RPFC (Chen et al., 2017) (mixture of Radix puerariae and Fructus crataegi) are reportedly inhibitors of tubuloe epithelial epithelial-mesenchymal transition (EMT). Curcumin (Lu et al., 2017), Epigallocatechin-3-gallate (Yang et al., 2016), Piperine (Samra et al., 2016), Gallic acid (Garud and Kulkarni, 2018), Luteolin (Wang et al., 2011), Baicalin (Yang et al., 2019), Loganin (Liu et al., 2015), Catapol (Chen et al., 2020), Berberine (Qiu et al., 2017; Zhang et al., 2020b), Zingerone (Cui et al., 2018), Coumarin (Sen et al., 2019), Ursolic acid (Xu et al., 2018a), Ellagic acid (Zhou et al., 2019), Puerarin (Xu et al., 2016), 6-Shogaol (Xu et al., 2018b), Betanin (Sutariya and Saraf, 2017), Betulinic acid (Sutariya et al., 2017), Emodin (Tian et al., 2018), Hispidulin (Wu et al., 2018) and Salvianolic acid (Hou et al., 2017) are some phytocompounds demonstrating a range of activities including reductions in AGE products, reduction of inflammation, inhibition of podocyte injury and apoptosis, reduced oxidative stress and endothelial cell dysfunction, inhibition of GMC expansion etc. which ultimately reduce the harshness of DN (Table-2 and Fig. 2). Google Scholar, SciFinder, Scopus and PubMed search engines were used to collect literature on DKD or DN and therapeutic targets in DN...

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Citation Excerpt :

...Similarly, 6-gingerol prevents osteoclast differentiation and represses IL-1-induced PGE2 synthesis in mouse osteoblasts.88 Moreover, zingerone restores the renal functions and declines the generation of TNF- α , IL-1 β , IL-6

and ROS in animal models of nephropathy.^{89,90} In addition, zerumbone downregulates TNF- α , IL-1 β , and IL-6 in an animal neuropathic pain model.⁹¹...

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2020, Journal of Functional Foods

Citation Excerpt :

...Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone; Fig. 1) is one of the major constituent of ginger root (*Zingiber officinale*, Roscoe) with multiple biological activities. This natural polyphenol has slightly spicy pungent odour but is considered harmless (Cui et al., 2018). Due to its potent anti-mitotic and anti-proliferative ability, zingerone has shown inhibition of cellular growth and suppression of tumor development including neuroblastoma cells, thereby suggesting that it may have promising anticancer therapy in humans (Ahmad, Rehman, Amin, Arif, Rasool, Bhat, & Bilal, 2015)....

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