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Attenuation of inflammatory response by a novel chalcone protects kidney and heart from hyperglycemia-induced injuries in type 1 diabetic mice

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ABSTRACT

High glucose-induced inflammatory response in diabetic complications plays an important role in disease occurrence and development. With inflammatory cytokines and signaling pathways as important mediators, targeting inflammation may be a new avenue for treating diabetic complications. Chalcones are a class of natural products with various pharmacological activities. Previously, we identified L2H17 as a chalcone with good anti-inflammatory activity, inhibiting LPS-induced inflammatory response in macrophages. In this study, we examined L2H17's effect on hyperglycemia-induced inflammation both in mouse peritoneal macrophages and a streptozotocin-induced T1D mouse model. Our results indicate that L2H17 exhibits a strong inhibitory effect on the expression of pro-inflammatory cytokines, cell adhesion molecules, chemokines and macrophage adhesion via modulation of the MAPK/NF-κB pathway. Furthermore, in vivo oral administration of L2H17 resulted in a significant decrease in the expression of pro-inflammatory cytokines and cell adhesion molecules, contributing to a reduction of key markers for renal and cardiac dysfunction and improvements in fibrosis and pathological changes in both renal and cardiac tissues of diabetic mice. These findings provide the evidence supporting targeting MAPK/NF-κB pathway may be effective therapeutic strategy for diabetic complications, and suggest that L2H17 may be a promising anti-inflammatory agent with potential as a therapeutic agent in the treatment of renal and cardiac diabetic complications.

Introduction

In the past few decades, metabolic syndrome and diabetes have become increasingly prevalent health issues. The complications of these disorders, such as cardiovascular diseases, stroke, peripheral vascular diseases, diabetic neuropathy, amputations, renal failure, and blindness, can result in increased disability, reduced life expectancy, and enormous health costs (Israili, 2011). Current treatment for diabetes has also been limited to and centered on controlling blood glucose, cholesterol and insulin levels, and the major drug categories used to treat diabetes have several major side effects and notable limitations in terms of safety, tolerability, and ease of use (Rotenstein et al., 2012). In addition, agents for the treatment of diabetes usually fail to treat diabetic complications. Therefore, the development of a new and effective drug category for the treatment of diabetic complications is pivotal.

In recent years, there has been increasing evidence indicating that inflammatory processes are involved in the development and progression of diabetic complications (Baumann et al., 2012; Calle and Fernandez, 2012; Devaraj et al., 2011; Eizirik et al., 2009; Maiti and Agrawal, 2007; Shoelson et al., 2003; Sonnett et al., 2010). Hyperglycemia is one of the key factors that contribute to diabetic complications (Brownlee, 1994; Vlassara et al., 1994; Lyons, 1993), and studies have shown that high glucose level can lead to the activation of transcription factor nuclear factor κB (NF-κB). NF-κB plays an important role in the regulation of pro-inflammatory genes (Guha et al., 2000; Shanmugam et al., 2003; Jain et al., 2003a, 2003b; Igarashi et al., 1999; Dandona et al., 2007; Yun et al., 2011), leading to the overproduction of inflammatory mediators, such as tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), interleukin-1β (IL-1β), cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), transforming growth factor (TGF)-β, and monocyte chemoattractant protein (MCP)-1 in the hearts and kidneys

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of diabetic rats (Guha et al., 2000; Shanmugam et al., 2003; Jain et al., 2003a, 2003b; Yun et al., 2011; Baker et al., 2011; Navarro-González and Mora-Fernández, 2008). The overexpressed cytokines and the infiltrated macrophages can then induce tissue stress, fibrosis, cell apoptosis, and organ injury. Therefore, agents that attenuate the inflammatory response may be useful in the clinical prevention and treatment of patients with diabetic complications.

Chalcones are a group of naturally occurring compounds that belong to the flavonoid family and are present in a variety of plant species, including fruits, vegetables, spices, tea and soy-based foodstuff (Wu et al., 2011). Chalcones have been shown to have a variety of pharmacological effects, including antioxidant, antimalarial, antitumor, anti-hyperglycemic, anti-inflammatory, and cardiovascular protective activity (Shukla et al., 2007; Hsieh et al., 2012; Fang et al., 2015). Chalcones can also be prepared synthetically, and the simplest chalcone can be prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of a base (Hsieh et al., 2012). Previously, we synthesized and evaluated a number of chalcone derivatives for

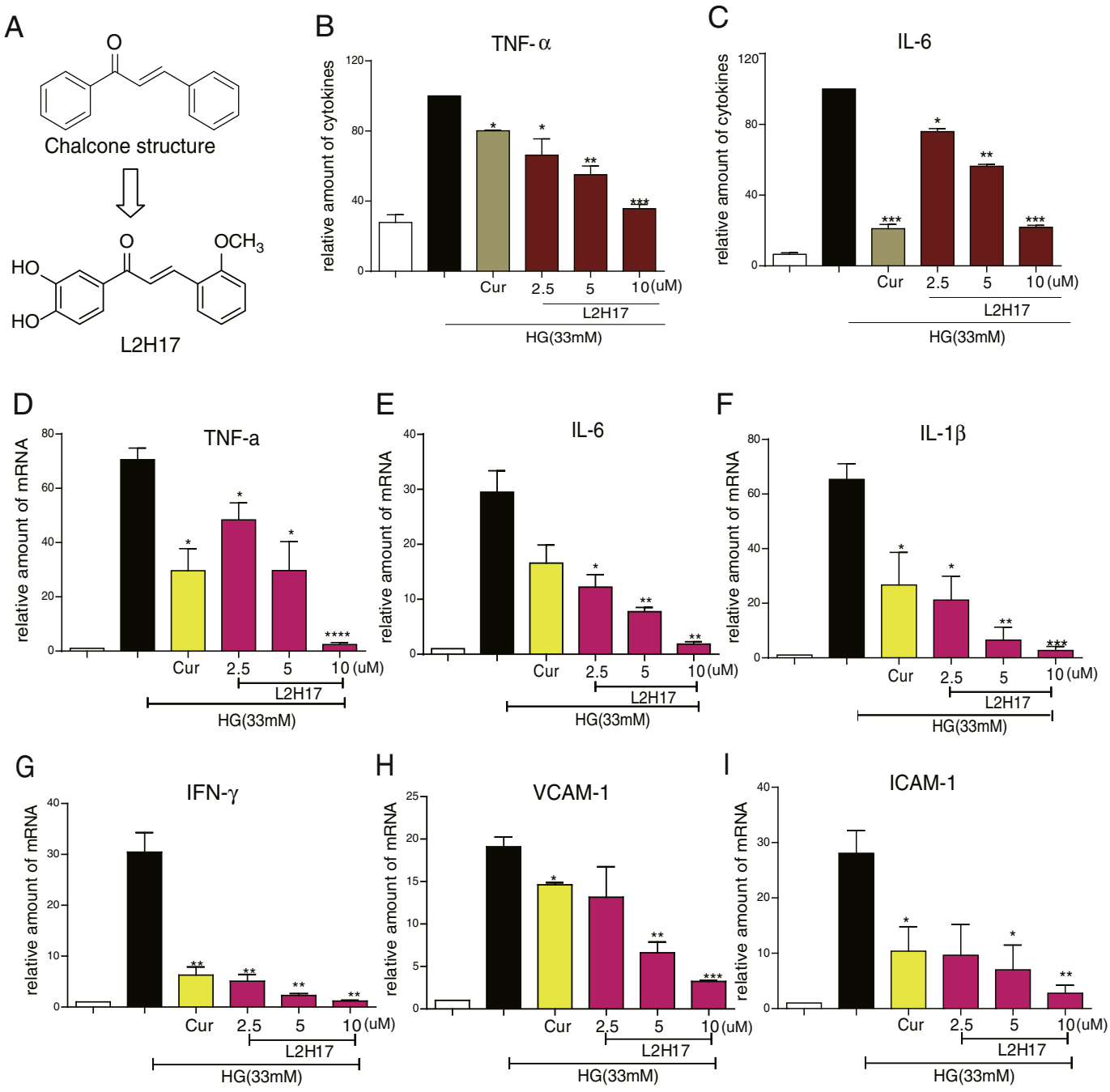

Fig. 1. L2H17 inhibited HG-induced expression of inflammatory cytokines and adhesion molecules. A. The chemical structures of chalcone and L2H17. (B–C) MPMs (1×10^6) were pretreated with L2H17 (2.5, 5 or 10 μM), curcumin (10 μM), or vehicle (DMSO, 3 μl) for 1 h and then stimulated with HG (33 mM) either for 24 h. The levels of TNF-α (B) and IL-6 (C) in the medium were detected by ELISA. (D–I) MPMs (1×10^6) were pretreated with L2H17 (2.5, 5 or 10 μM), curcumin (10 μM), or vehicle (DMSO, 3 μl) for 1 h and then stimulated with HG (33 mM) either for 12 h. The total RNA was extracted and the mRNA levels of TNF-α (D), IL-6 (E), IL-1β(F), IFN-γ(G), VCAM-1(H) and ICAM-1(I) were detected by real-time qPCR assay. Bars represent the mean ± SEM of these independent experiments performed in duplicate, and asterisks indicate significant inhibition (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. the HG group).