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PhD Dissertation Defense

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TO STUDY THE ROLE OF CB2 RECEPTOR AGONISTS IN EXPERIMENTAL MODELS OF DIABETES COMPLICATIONS

by

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Yanah Theater, Second Floor, Block C (2C010), Male Side, CMHS

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Abstract

Diabetes mellitus (DM) and its associated complications are considered one of the serious risks to contemporary society. Amongst numerous complications, diabetic cardiomyopathy (DCM) is characterized by the increased accumulation of lipids, and reduced glucose utilization following abnormal lipid metabolism in myocardium along with oxidative stress, myocardial fibrosis, and inflammation, that eventually results in cardiac dysfunction. The cannabinoid 2 receptors (CB2) have a crucial role in the management of obesity, hyperlipidemia, and diabetes mellitus. Provided the role of CB2 receptors in regulating glucolipid metabolic dysfunction, its antioxidative, antifibrotic, and anti-inflammatory effects, we designed the present study to investigate protective effects and underlying mechanism of a selective CB2 receptor agonist, β-Caryophyllene (BCP), a dietary cannabinoid in murine model of DCM. Mice were fed a high-fat diet for 4 weeks followed by a single dose of streptozotocin (100 mg/kg) injection to develop the model of DCM. BCP (50 mg/kg body weight) was administered orally for 12 weeks. AM630 a specific CB2 antagonist, was given 30 min before BCP treatment to demonstrate the CB2 receptor dependent mechanism of BCP. BCP treatment significantly improved glucose tolerance, insulin resistance, enhanced serum insulin level, and decreased the elevated blood glucose level. BCP also reversed the lipid profile derangement and alleviated lipid accumulation in the heart tissue of DCM mice. BCP reversed cardiac remodeling, mitigated cardiac injury, and restored cardiac contractile function. Furthermore, ultrastructural examination showed that myocardial cell injury was decreased in the DCM mice treated with BCP. This improvement was associated with reduced expression of AGE/RAGE in DCM mice hearts. BCP significantly relieved oxidative stress through inhibition of NOX4 expression and activation of PI3K/AKT/Nrf2 signaling. Also, BCP suppressed cardiac fibrosis and endothelial-to-mesenchymal transition (EndMT) in DCM mice hearts through inhibition of TGF-β/Smad signaling. BCP significantly attenuated myocardial inflammation and decreased production of proinflammatory cytokines and inflammatory enzyme mediators via inhibition of TLR4/NF-κB/MAPK signaling. NLRP3 inflammasome activation was suppressed in DCM mice treated with BCP. Additionally, BCP alleviated pancreatic damage and significantly elevated the number of insulin-positive cells. Interestingly, pre-administration of the CB2 receptor antagonist AM630 abrogated the positive effects of BCP in DCM mice. Collectively, BCP has the potential to protect the myocardium and pancreas of DCM mice in a CB2 receptor dependent mechanism.

Keywords: Cannabinoid 2 receptors, β-Caryophyllene, diabetic cardiomyopathy, lipotoxicity, oxidative stress, inflammation, fibrosis, inflammasome.