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Research paper

Hydroxylated polymethoxyflavones reduce the activity of pancreatic lipase, inhibit adipogenesis and enhance lipolysis in 3T3-L1 mouse embryonic fibroblast cells

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ABSTRACT

Hydroxylated polymethoxyflavones (HPMFs) have been shown to possess various anti-disease effects, including against obesity. This study investigates the anti-obesity effects of HPMFs in further detail, aiming to gain understanding of their mechanism of action in this context. The current study demonstrates that two HPMFs; 3′-hydroxy-5,7,4′,5′-tetramethoxyflavone (**3′OH-TetMF**) and 4′-hydroxy-5,7,3′,5′-tetramethoxyflavone (**4′OH-TetMF**) possess anti-obesity effects. They both significantly reduced pancreatic lipase activity in a competitive manner as demonstrated by molecular docking and kinetic studies. In cell studies, it was revealed that both of the HPMFs suppress differentiation of 3T3-L1 mouse embryonic fibroblast cells during the early stages of adipogenesis. They also reduced expression of key adipogenic and lipogenic marker genes, namely peroxisome proliferator-activated receptor-gamma (PPARγ), CCAAT/enhancer-binding protein α and β (C/EBP α and β), adipocyte binding protein 2 (aP2), fatty acid synthase (FASN), and sterol regulatory element-binding protein 1 (SREBF 1). They also enhanced the expression of cell cycle genes, i.e., cyclin D1 (CCND1) and C-Myc, and reduced cyclin A2 expression. When further investigated, it was also observed that these HPMFs accelerate lipid breakdown (lipolysis) and enhance lipolytic genes expression. Moreover, they also reduced the secretion of proteins (adipokines), including pro-inflammatory cytokines, from mature adipocytes. Taken together, this study concludes that these HPMFs have anti-obesity effects, which are worthy of further investigation.

1. Introduction

Obesity is a worldwide health issue; it is now being recognized as a lifestyle disorder in the developing world, while its prevalence has already reached an alarming level in developed countries [1]. According to the 2017 Global Burden of Disease study, more than 4 million deaths were attributed to being overweight or obese that year. This trend of overweight and obesity was tracked from 1975 to 2016 and it was found to have increased more than 4-fold, from 4% to 18% globally [2,3]. Obesity contributes to metabolic syndrome, numerous cancers, cardiovascular disease, fatty liver, type II diabetes and insulin resistance [4,5]. It arises due to excess energy intake compared with energy expenditure, leading to excessive fat accumulation in adipose tissue [6]. Pancreatic lipase (PL) is crucial for the absorption and digestion of dietary fats [7,8], and hydrolyzes 50–70% of the total dietary fats in the digestive system [9–11]. PL inhibition changes the absorption and digestion of ingested triglycerides and is therefore the most widely studied mechanism for screening anti-obesity agents [12,13]. In obesogenic

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