**In Vitro Regulation of Enzymes of the Renin-angiotensin-aldosterone System by Isoquercitrin, Phloridzin and their Long Chain Fatty Acid Derivatives**

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**ABSTRACT**

**Background:** Hypertension is a crucial risk factor for development of cardiovascular and neurological diseases. Flavonoids exhibit a wide range of biological effects and have had increased interest as a dietary approach for the prevention or possible treatment of hypertension. However, continuous efforts have been made to structurally modify natural flavonoids with the hope of improving their biological activities. One of the methods used for the possible enhancement of flavonoid efficacy is enzymatic esterification of flavonoids with fatty acids.

**Objective:** The current study is designed to investigate the antihypertensive activity of isoquercitrin (quercetin-3-O-glucoside, Q3G) and phloridzin (PZ) in comparison to their twelve long chain fatty acid derivatives via enzymatic inhibition of renin angiotensin aldosterone system (RAAS) enzymes.

**Methods:** The novel flavonoid esters were synthesized by the acylation of isoquercitrin and phloridzin with long chain unsaturated and saturated fatty acids (C18–C22). These acylated products were then tested for their in vitro angiotensin converting enzyme (ACE), renin and aldosterone synthase activities.

**Results:** The linoleic and α-linolenic acid esters of PZ were the strongest (IC$_{50}$ 69.9-70.9 µM) while Q3G and PZ (IC$_{50}$ >200 µM) were the weakest renin inhibitors in vitro (p≤0.05). The eicosapentaenoic acid ester of PZ (IC$_{50}$ 16.0 µM) was the strongest inhibitor of ACE, while PZ (IC$_{50}$ 124.0 µM) was the weakest inhibitor (p≤0.05) among all tested compounds. However, all investigated compounds had low (5.0-11.9%) or no effect on aldosterone synthase inhibition (p≤0.05). The parent compound Q3G and the eicosapentaenoic acid ester of PZ emerged as the strongest ACE inhibitors.
Conclusions: The structural modification of Q3G and PZ significantly improved their antihypertensive activities. The potential use of PZ derivatives as natural health products to treat hypertension needs to be further evaluated.

Keywords: hypertension, phloridzin, isoquercitrin, flavonoids, ACE, renin, RAAS, acylation, fatty acids