Plant flavonoids as angiotensin converting enzyme inhibitors in regulation of hypertension

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Submission date: March 6, 2011; Acceptance date: May 6, 2011; Publication date: May 8, 2011

Abstract

Background: Angiotensin converting enzyme (ACE) is a key component in the renin angiotensin aldosterone system (RAAS) which regulates blood pressure. As the over expression of RAAS is associated with vascular hypertension, ACE inhibition has become a major target control for hypertension. The research on potential ACE inhibitors is expanding broadly and most are focused on natural product derivatives such as peptides, polyphenolics, and terpenes. Plant polyphenolics are antioxidant molecules with various beneficial pharmacological properties. The current study is focused on investigating and reviewing the ACE inhibitory property of fruit flavonoids. An apple skin extract (ASE) rich in flavonoids, the major constituents of the extract and their selected metabolites were assessed for the ACE inhibitory property in vitro. It is important to investigate the metabolites along with the flavonoids as they are the constituents active inside the human body.

Objective: To investigate whether flavonoids, flavonoid rich apple extracts and their metabolites could inhibit ACE in vitro.

Method: The samples were incubated with sodium borate buffer (30 µL, pH 8.3), 150 µL of substrate (Hip-His-Liu) and ACE (30 µL) at 37 °C for 1 h. The reaction was stopped by addition of 150 µL of 0.3M NaOH. The enzyme cleaved substrate was detected by making a fluorimetric
adduct by adding 100 µL of o-phthaldehyde for 10 min at room temperature. Reaction was stopped by adding 50 µL of 3M HCl. Fluorescence was measured by using a FluoStar Optima plate reader at excitation of 350 nm and emission of 500 nm.

**Results:** The extract and the compounds showed a concentration dependant enzyme inhibition. Increasing concentrations from 0.001 ppm to 100 ppm of ASE showed an increment of 29% to 64% ACE inhibition. The IC<sub>50</sub> (concentration of test compound which gives 50% enzyme inhibition) values of ASE, quercetin, quercetin-3-glucoside, quercetin-3-galactoside, cyanidin-3-galactoside were 49 µg/mL, 151 µM, 71 µM, 180 µM, 206 µM, respectively. The major constituents of the ASE that were tested separately showed effective ACE inhibition. From the three metabolites tested, only quercetin-3-glucuronic acid showed concentration dependant ACE inhibition. The ACE inhibition of 0.001 ppm to 100 ppm of quercetin-3-glucuronic was in the range of 43% and 75% and the IC<sub>50</sub> value was 27 µM.

**Conclusion:** The results demonstrated that flavonoids have a potential to inhibit ACE *in vitro* and the inhibitory property varies according to type of sugar moiety attached at C-3 position. The results also revealed that the major contributing compounds of ASE for ACE inhibition belong to flavonoids. Among the tested compounds, the lowest IC<sub>50</sub> value is associated with the quercetin-3-glucuronic acid, a major *in vivo* metabolites of quercetin and its glycosides. The results suggest that certain dietary flavonoids may possess properties of blood pressure regulation.

**Key words:**
Hypertension, renin angiotensin system (RAS), angiotensin converting enzyme (ACE), flavonoids, apple