Binding of the commonly used antioxidants (quercetin, resveratrol, and dihydrolipoic acid) to major circulating proteins – spectroscopic and *in silico* docking and molecular dynamic simulation studies

Abstract

Poor bioavailability and reduced stability are the main drawbacks to efficiently utilizing many naturally occurring antioxidants, so their binding to circulatory proteins is essential. This work investigated whether major human circulatory proteins, besides albumin, including transferrin, alpha-2-macroglobulin, and fibrinogen, bind widely consumed antioxidants and food supplements, including quercetin, *trans*-resveratrol, and dihydrolipoic acid, thus filling the gap of detailed pharmacokinetic properties of these food supplements. Detailed examination of the protein structural and functional changes that occur upon ligand binding was analyzed by spectroscopic methods and *in silico* docking and molecular dynamic simulation studies on the model that consists of the protein/antioxidant pair with the highest affinity constant. It was found that alpha-2-macroglobulin binds *trans*-resveratrol with the highest affinity (K_a of 4.5 x 10^4 M^{-1}). *In silico* results revealed four potential binding sites between *trans*-resveratrol and alpha-2-macroglobulin, with hydrogen bonds being crucial for binding, while other observed interactions (primarily aromatic interactions) are of secondary importance. The binding of *trans*-resveratrol to alpha-2-macroglobulin leads to mutual protection of both molecules from oxidative stress and significantly increased hidrosolubility of resveratrol, both of which could serve to increase the bioavailability and bioactivity of resveratrol in circulation.