Synopsis of Original Research Paper

Tyrosinase-catalyzed oxidation of resveratrol produces a highly reactive *ortho*-quinone: implications for melanocyte toxicity

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trans-Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene, RES), a naturally occurring polyphenol, is well known for its antioxidant, anti-platelet, anti-inflammatory, anti-aging, cardioprotective and cancer chemopreventive properties and has recently attracted increased interest as a health-beneficial agent. However, the recent incidence of rhododendrol-induced leukoderma highlights the risk of using compounds having *p*-substituted phenols because of their rapid conversion to toxic *o*-quinones. Based on its *p*-substituted phenol structure, RES is also expected to be a substrate for tyrosinase and to produce a toxic *o*-quinone metabolite. In fact, RES was found to be a good substrate for tyrosinase. The results of this study demonstrate that the oxidation of RES by tyrosinase produces 4-(3',5'-dihydroxy-*trans*-styrenyl)-1,2-benzoquinone (RES-quinone), which decays rapidly to an oligomeric product (RES-oligomer). RES-quinone was identified after reduction to its corresponding catechol, known as piceatannol. RES-quinone reacts with *N*-acetylcysteine, a small thiol, to form a diadduct and a triadduct, which were identified by NMR and MS analyses. The production of a triadduct is not common for *o*-quinones, suggesting a high reactivity of RES-quinone. RES-quinone also binds to bovine serum albumin through its cysteine residue. RES-oligomer can oxidize GSH to GSSG, indicating its pro-oxidant activity. These results suggest that RES could be cytotoxic to melanocytes due to the binding of RES-quinone to thiol proteins and the cosmetic use of RES should be considered with caution. Equol (7,4-dihydroxy-isoflavan) is one of the end products of the intestinal bacterial biotransformation of the isoflavone daidzein which is phytoestrogen found in soy and soy-derived products, and a nonsteroidal estrogen of the isoflavone family. Equol is not a natural constituent of plants, but established as a bacterial metabolite of daidzein. Since equol has the *p*-substituted phenol structure as well as RD and RES, it is expected to be a substrate for tyrosinase and to produce a toxic *o*-quinone metabolite. In order to examine whether equol produces the *o*-quinone, we performed the tyrosinase-catalyzed oxidation of equol. UV/visible spectra showed the unstable quinone absorption at 420 nm within 15 min. Converting the *o*-quinones produced by tyrosinase oxidation of equol in the presence of ascorbic acid to more stable catechols, we could obtain three compounds by preparative HPLC at UV detection. Although these compounds have been known to be metabolized from equol using human liver microsomes, it is the first time that these compounds are formed by tyrosinase-catalyzed oxidation of equol.