Supplementary Methods

Concentration of resveratrol and its metabolites

The concentrations of resveratrol and its metabolites including resveratrol 3-O-glucuronide, resveratrol 4-O-glucuronide, and resveratrol 3-O-sulfate in patients who provided a written informed consent for the National Cerebral and Cardiovascular Center (NCVC) biobank were measured. The liquid chromatography-mass spectrometry (LC-MS) quantification was performed using a mass spectrometer (Xevo TQ-XS; Waters, Milford, MA, USA) coupled to a liquid chromatography (UPLC I-Class, Waters) using resveratrol (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan); trans-resveratrol 3-sulfate sodium salt (Toronto Research Chemicals, Toronto, ON, Canada); and trans-resveratrol 3-O-β-D-glucuronide, trans-resveratrol 4'-O-β-D-glucuronide, and trans-resveratrol-d4 (Cayman Chemical, Ann Arbor, MI, USA).

The protocol for the determination of resveratrol and its metabolites in human plasma was as follows. Initially, the solid phase extraction (SPE) cartridge (Oasis HLB 96-well μElution plate 2 mg; Waters) was conditioned with 200 μL of 2% formic acid followed by 200 μL of methanol. Subsequently, 200 μL of samples two-fold diluted internal standard solution (100 ng/mL of trans-resveratrol-d4 in 2% formic acid) loaded on the SPE cartridge, followed by washing the SPE cartridge with 200 μL of 2% formic acid. Finally, analytes were eluted twice with 100 μL of methanol/ammonia solution 28% (19:1). After centrifugation (500×*g*, 30 sec, 4°C), supernatants were dried for 20 min at 40°C under a nitrogen stream. The residues were reconstituted in 150 μL of 10 mM ammonium formate in water/methanol (9:1) and subjected to analysis.

We used a YMC Triart C18 column (3 μm, 3.0×50 mm, YMC, Kyoto, Japan) kept at 40°C for LC separation and the injected sample volume was 2 μL. The mobile phases A and B were 10 mM ammonium formate in water and acetonitrile, respectively. The flow rate was 2 mL/min, following the multistep gradient methods. The concentration of mobile phase B was increased from 10% to 90% at 7 min, and then decreased to 10% at 7.5 min, and equilibrated for 4.5 min. MS/MS with electrospray ionization was operated in negative ionization multiple-reaction monitoring mode and the transitions monitored were m/z (mass-to-charge ratio) 227 to 185 (resveratrol), m/z 403 to 113 (resveratrol 3-O-glucuronide and resveratrol 4-O-glucuronide), m/z 307 to 227 (resveratrol 3-O-sulfate) and m/z 231 to 189 (trans-resveratrol-d4).