学 位 論 文 の 要 旨

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主論文の題名

Myricetin causes site-specific DNA damage via reactive oxygen species generation by redox interactions with copper ions

主論文の要旨

Myricetin (MYR), a flavonoid, may have preventive effects on Alzheimer's disease and cancer. However, MYR is also mutagenic inducing DNA damage in the presence of metal ions. We have studied the molecular mechanisms of DNA damage by MYR in the presence of Cu(II) (MYR+Cu). MYR+Cu caused concentration-dependent DNA strand breaks and base alterations in ^{32}P-5′-end-labeled DNA, leading to cleavage of DNA at thymine, cytosine, and guanine nucleotides. Formation of the oxidative DNA damage indicator, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), in calf thymus DNA was increased by MYR+Cu. The production of 8-oxodG in MYR-treated HL-60 cells was significantly higher than in HP100 cells, which are more resistant to H_2O_2 than are HL-60 cells. Reactive oxygen species (ROS) scavengers were used to elucidate the mechanism of DNA damage. DNA damage was not inhibited by typical free hydroxyl radical (•OH) scavengers such as ethanol, mannitol, or sodium formate. However, methional, catalase, and bathocuproine inhibited DNA damage induced by MYR+Cu. These results suggest that H_2O_2, Cu(I), and ROS other than •OH are involved in MYR+Cu-induced DNA damage. We conclude that the Cu(I)/Cu(II) redox cycle and concomitant H_2O_2 production via autoxidation of MYR generate a complex of H_2O_2 and Cu(I), probably Cu(I)-hydroperoxide, which induces oxidative DNA damage.