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ANTIMUTAGENICITY OF DIETARY AND MEDICINAL FLAVONOLS IN HUMAN DERIVED METABOLICALLY COMPETENT HEPATOMA CELLS

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Flavonols are polyphenolic compounds that are present in dietary plant-based foodstuffs and beverages (e. g. apple, onion, grape fruit, tea) and medicinal plants (e. g. Crategus, Ruta graveolens, Silybum marianum, Fagopyrum species) in high concentrations. They have been reported to exhibit a wide variety of biological effects, including anti-inflammatory, antiviral, antioxidant and free-radical-scavenging activities. Furthermore, they may have cancer protective effects in humans which consume vegetables and/or fruits rich in flavonoids. In the present study the mutagenic and antimutagenic effects of the flavonols Fisetin, Kaempferol, Myricetin and Quercetin were studied in the human derived hepatoma cell line Hep G2. As a biological endpoint we examined the frequency of single strand breaks using the single cell gel electrophoresis (SCGE, syn. Comet assay). The flavonols were tested alone and in combination with benzo[a]pyrene (B[a]P), which is considered to be a mutagen and human carcinogen. The potency of the flavonols to modulate or to inhibit the genotoxic activity of (±)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE), the ultimate mutagen/carcinogen of B[a]P, was also investigated. Exposure of Hep G2 cells to flavonols increased induction of DNA damage at concentrations of 50 μM (P <0.01) and 100 μM (P <0.001) in comparison to the solvent (DMSO) control. Exposure of B[a]P for 24 h resulted in dose-dependent, significant (P <0.01) DNA damages. In the combination assay Hep G2 cells were exposed to increasing concentrations of Fisetin, Kaempferol, Myricetin and Quercetin (1250 μM) for 24 h prior

to the exposure to B[a]P (50 μM) for further 24 h. The treatment of Hep G2 cells with the bioflavonoids prior to B[a]P exposure significantly (P <0.05 and P <0.01) protected the cells against B[a]P-induced DNA damages in a dose-dependent manner. In all cases, pronounced antimutagenic effects were observed. The inhibition efficacies measured as the decrease of Olive Tail Moment (OTM) in SCGE using flavonol concentrations of 100 μM were in the order Kaempferol (99 %) > Fisetin (94 %) > Quercetin (88 %) > Myricetin (68 %). In combination experiments with BPDE also a pronounced protection was found: All flavonols reduced the activity of BPDE under the same experimental conditions but to a higher degree as in the B[a]P trials. The experiments showed that the four flavonols investigated are effective in reducing the mutagenic activity of both the promutagen/procarcinogen B[a]P and its active metabolite BPDE in human derived cells even at low concentrations. The results suggested that these protective effects of the flavonols are mainly due to the inactivation (scavenging) of the ultimate mutagen, i.e. diol epoxide of B[a]P. Based on these results and on the results of previous investigations, foodstuffs or medicinal plants containing bioflavonoids like Fisetin, Kaempferol, Myricetin and Quercetin may suppress the activity of ultimate mutagens/carcinogens and therefore may be useful for the chemoprevention of cancer. The studies were supported by the EC grant QLK1-CT-1999-0810 and HEEL Germany