Mechanisms by which fruit polyphenols act as cancer chemopreventive agents

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Introduction

Regular consumption of fruit and vegetables correlates with a decreased incidence of cancer. Polyphenols are thought to contribute to this and their chemopreventive effect may relate to their ability to induce genes for antioxidant and detoxification enzymes, such as NAD(P)H:quinone oxidoreductase (NQO1), possibly through the antioxidant response element (ARE) and/or the xenobiotic response element (XRE). Our study has examined the mechanisms putatively responsible for a polyphenol-derived cancer chemoprevention effect with specific focus on Nrf2, a redox-sensitive transcription factor and CYP1A1, a member of the cytochrome P450 superfamily, known to operate as an arylhydrocarbon hydroxylase. The flavonols quercetin and kaempferol were used as model polyphenols for our studies.

Hypothesis

At what point in the body’s antioxidant and detoxification systems do plant polyphenols exert their action, if at all?

Experimental Approach and Results

1. Quercetin and Kaempferol Can Increase the Expression of NQO1
2. The Involvement of ARE and XRE in the Induction of NQO1 by Quercetin and Kaempferol.
3. Quercetin and Kaempferol can increase the expression of Nrf2 at the protein level but have no effect on the mRNA level.
4. Quercetin and Kaempferol alter the intracellular localization and localization of Nrf2.
5. CHX chase experiment was carried out in the presence and absence of either Quercetin or Kaempferol to showing both chemicals can increase the half life of Nrf2 protein in RL34 cells
6. Quercetin and Kaempferol increase mRNAs of CYP1A1 and AhR
7. Quercetin can increase the gene expression of CYP1A1 in mouse small intestine

Conclusion

Quercetin and Kaempferol can increase the expression of antioxidant and detoxification enzymes NQO1 and CYP1A1.

The induction of NQO1 is dependent on ARE and partially on XRE.

Induction is regulated by Nrf2 which can be stabilized by Quercetin and Kaempferol.

Furthermore, intervention studies with mice using Quercetin at 10mg/kg for 4 days saw an associated increase in CYP1A1 mRNA level in the mouse’s small intestine perhaps suggesting positive benefits with regard to risk of digestive tract cancers.

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