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Targeting of increased copper level in diethylnitrosamine (DEN) induced hepatocellular carcinoma cells in rats by epigallocatechin-3-gallate (EGCG)

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To account for the observed anticancer properties of plant polyphenols, we have proposed a mechanism which involves the mobilization of endogenous copper ions by polyphenols leading to the generation of reactive oxygen species (ROS) that serve as proximal DNA cleaving agents. Over the last decade, we have proceeded to validate our hypothesis with considerable success. For example, polyphenol induced growth inhibition in breast cancer cell lines is inhibited by copper chelators and copper overload in lymphocytes leads to increased cellular DNA degradation by polyphenols. As a further confirmation of our hypothesis, we have induced hepatocellular carcinoma in rats by diethylnitrosamine (DEN). The induction of carcinoma was confirmed by visual examination of liver and various liver cancer markers. We show that in such carcinoma cells there is a progressive elevation in copper levels at various intervals after DEN administration. Concurrently with increasing copper levels epigallocatechin-3-gallate [(EGCG), a potent anticancer plant polyphenol found in green tea], mediated DNA breakage in malignant cells is also increased. This is further confirmation of the increased copper levels in such cells. The cell membrane permeable copper chelator neocuproine inhibited the EGCG mediated cellular DNA degradation whereas the membrane impermeable chelator bathocuproine was ineffective. Iron and zinc specific chelators desferrioxamine mesylate and histidine respectively were also ineffective in inhibiting EGCG mediated DNA breakage.

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