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The health benefits of plant derived polyphenols including resveratrol, epigallocatechin-3-gallate, delphinidin, caffeic acid, curcumin, capsaicins, tannins and flavonoids have been attributed to their antioxidant effects. However, there is evidence in literature suggesting that antioxidant activity of such plant derived polyphenols may not fully account for their chemopreventive effects. Therefore, it is plausible that other mechanisms may be responsible for the varied pharmacological properties. Most antioxidants of plant origin are redox (reduction-oxidation) agents, protecting against ROS generation in some cases and promoting radical generation in others (Herbert, 1996). Studies in this laboratory have shown that plant polyphenols behave as prooxidants in the presence of copper ions, catalyzing DNA breakage through the generation of reactive oxygen species (Ahmad et al., 1992; Bhat and Hadi, 1994; Ahsan and Hadi, 1998; Ahmad et al., 2000; Azam et al., 2004; Ahmad et al., 2005). Copper is a major metal ion present in the nucleus and is also implicated in tumorigenesis and angiogenesis (Chevion, 1988). Oxidative DNA breakage by these compounds correlates with their apoptosis inducing capacity. Further, properties of polyphenols, such as binding and cleavage of DNA and the generation of ROS in the presence of transition metal ions are similar to those of some known anticancer drugs (Ehrenfeld et al., 1987). Serum, tissue and cellular copper levels are significantly elevated in a number of malignancies (Linder, 1991; Gupte and Mumper, 2009). Red wine and green tea are known good sources of the polyphenols resveratrol and EGCG respectively. Induction of apoptosis by resveratrol as well as EGCG has been shown in various human cancer cell lines (Clement et al., 1998; Ahmad et al, 1997).

There is significant data in literature that points to the prooxidant rather than the antioxidant property of polyphenols as the mechanism of their anticancer
properties. Taking into consideration our own observations and those of others we have proposed a mechanism according to which plant polyphenols mobilize endogenous copper in cancer cells leading to cytotoxic action through the generation of reactive oxygen species (Hadi et al., 2000; Hadi et al., 2007). Based on the above hypothesis, in the work presented here, I have attempted to elucidate the mechanism of action of plant derived polyphenolic compounds; specially the stilbene resveratrol, flavonol EGCG and hydroxyanthraquinones aloin and aloe-emodin. Using a cellular system of human peripheral lymphocytes and alkaline single cell gel electrophoresis (Comet Assay), I have confirmed that polyphenol-Cu(II) system is indeed capable of causing DNA degradation in cells such as lymphocytes. These findings demonstrate that polyphenol-Cu(II) system for DNA breakage is physiologically feasible and could be of biological significance. Experiments done in this laboratory has already shown that these polyphenols alone (in the absence of added Cu(II)) are also capable of DNA breakage in intact lymphocytes which is inhibited by the scavengers of reactive oxygen and neocuproine (a membrane permeable Cu(I) specific sequestering agent). Bathocuproine, which is unable to permeate through the cell membrane, did not cause such inhibition. Using lysed version of Comet assay, I have further shown that polyphenols are able to degrade DNA in cell nuclei and that such DNA degradation is inhibited by neocuproine as well as bathocuproine (both of which are able to permeate the nuclear pore complex), suggesting that nuclear copper is mobilized in this reaction. However since the lysed version required the preparation of cell nuclei at an alkaline pH, there existed a possibility that the DNA might undergo some structural changes which may be responsible for the enhanced DNA breakage. In order to rule out the possibility of such a structural change in cellular DNA, I have prepared permeabilized cells at neutral pH (Czene et al, 1997), thereby eliminating the need for pretreatment of cells at an alkaline pH and allowing the polyphenols to interact with cell nuclei at
physiological pH. The results obtained with permeabilized cellular system were similar to the results obtained using lysed version (Shamim et al., 2008). These results are in further support of the hypothesis that anticancer mechanisms of plant polyphenols may involve mobilization of endogenous copper, possibly nuclear copper and the consequent prooxidant action.