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The health benefits of plant-derived polyphenols including caffeic and \( p \)-coumaric acids, resveratrol, curcumin, capsaicins, tannins and flavonoids have been attributed to their antioxidant effects. There is evidence in literature suggesting that antioxidant activity of such plant derived polyphenols may not fully account for their chemopreventive effects. This is because 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). Therefore, it is plausible that other mechanisms may also be responsible for such varied pharmacological properties. 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; Ahsan & Hadi, 1998; Bhat & Hadi, 1994; Ahmad et al., 2000; Azam et al., 2004; Ahmad et al., 2005). 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). Copper is the major metal ion present in the nucleus and it is also implicated in tumorigenesis and angiogenesis (Chevion et al., 2000). Also, serum, tissue and cellular copper levels are elevated in numerous malignancies (Linder, 1991). It is well known that coffee is a good source of caffeic acid and it is also a constituent of wine. Caffeic acid has been shown to induce apoptotic cell death in human promyelocytic leukemia HL60 cells (Satoh & Sakagami, 1997) as well as in human hepatocarcinoma BEL-7402 cell line (Xu et al., 2005).

There is extensive data in literature that points to prooxidant rather than antioxidant property of polyphenols as the mechanism of their anticancer
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properties. Taking into consideration our own observations and those of others we have proposed a hypothesis 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). Based on the above hypothesis, in the work presented here I have tried to elucidate the mechanism of action of plant derived polyphenolic compounds specially the hydroxycinnamate caffeic acid. In this thesis using a cellular system of human peripheral lymphocytes isolated from human blood and alkaline single cell gel electrophoresis (Comet assay), I have confirmed that caffeic acid-Cu(II) system is indeed capable of causing DNA degradation in cells such as lymphocytes. Further, DNA degradation of lymphocytes is inhibited by scavengers of reactive oxygen and neocuproine which is a Cu(I) specific sequestering agent. These findings demonstrate that caffeic acid-Cu(II) system for DNA breakage is physiologically feasible and could be of biological significance. Experiments also show that caffeic acid alone (in the absence of added Cu(II)) is also capable of lymphocyte DNA breakage and that such breakage is mediated through mobilization of endogenous copper. These results are in further support of the hypothesis that anticancer mechanisms of plant polyphenols may involve mobilization of endogenous copper, possibly chromatin bound copper and the consequent prooxidant action (Azmi et al., 2005 & 2006).