SCOPE OF THE WORK
The health benefits of plant-derived polyphenols including resveratrol, curcumin, capsaicins, tannins and flavonoids have been attributed to their antioxidant effects. There is evidence in literature suggesting that antioxidant activity of such polyphenols may not fully account for their chemopreventive effects. This is because every antioxidant including resveratrol is a redox (oxidation-reduction) agent, 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 generation of reactive oxygen species (Ahmad et al., 1992; Ahsan & Hadi, 1998; Bhat & Hadi, 1994; Singh et al., 2001; Ahmad et al., 2000; Azam et al., 2004 and 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., 2003). Also, serum, tissue and cellular copper levels are elevated in numerous malignancies (Linder, 1991; Margalioth et al., 1983). It is well known that red wine is a good source of resveratrol. Additionally wines are also good sources of copper (Carno, 1988; Darret et al., 1986). It has also been shown that programmed cell death induced by resveratrol in THP-1 human monocytic leukemia cells is independent of Fas signaling pathway (Tsan et al., 2000) suggesting pathways other than 'classical'.

There is extensive data in literature that points to a prooxidant rather than an 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 hypothesis according to which plant polyphenols mobilize endogenous copper leading to cytotoxic action through 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 stilbene resveratrol. 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 resveratrol-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 a Cu(I) specific sequestering agent. These findings demonstrate that resveratrol-Cu(II) system for DNA breakage is physiologically feasible and could be of biological significance. Experiments also show that polyphenols alone (in the absence of added Cu(II)) are also capable of lymphocyte DNA breakage and that such breakage is mediated through mobilization of endogenous copper. These results are in further support of our hypothesis that anticancer mechanisms of plant polyphenols involve mobilization of endogenous copper, possible chromatin bound copper and the consequent prooxidant action (Azmi et al., 2005; Azmi et al., 2006).