Scope of the work presented
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Epidemiological studies have provided compelling evidence that link cancer risk to food habits. It has been recognized that the active principle of plant products are mainly the secondary metabolites. There are many nutritive and non-nutritive plants and their components that are under investigation for their potential cancer chemopreventive effects. The health benefits of such plant derived small molecules, such as terpenes and terpenoids, polyphenols and carotenoids have been attributed to their antioxidant effects. However, evidence in the literature suggests that the antioxidant activity of such plant molecules may not fully account for their chemopreventive and anticancer effects. Therefore, it is likely that other mechanisms may be responsible for their varied pharmacological properties.

Studies in this laboratory have shown that plant derived antioxidants such as polyphenols and ascorbic acid 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 tumorgenesis and angiogenesis (Chevion et al., 1988). Moreover, it is known that the serum, tissue and cellular levels of copper are significantly elevated in a number of malignancies (Linder, 1991; Gupte and Mumper, 2008). Taking into consideration our own observations and those of others we have proposed a mechanism according to which polyphenolic antioxidants 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). Towards the validation of our hypothesis, considerable evidence has been deduced over the years (Azmi et al., 2007; Hanif et al., 2008; Shamim et al., 2008; Ullah et al., 2009; Khan et al., 2011).

Based on the above hypothesis, in the work presented, I have attempted to elucidate the mechanism of action of two plant derived antioxidant molecules,
specifically gossypol and thymoquinone. Moreover, I have also assessed the activity of apogossypolone, a semi-synthetic derivative of gossypol, and compared it with its parent molecule. Using a cellular system of isolated peripheral human lymphocytes (comet assay), it was confirmed that these antioxidants are indeed capable of causing copper mediated DNA breakage. Thus, gossypol and ApoG2, as well as TQ fall under the category of plant polyphenols such as flavonoids, catechins etc (considered to possess anticancer properties) that are able to mobilize endogenous copper leading to the formation of reactive oxygen species and consequent cellular DNA breakage (Hadi et al., 2000; Hadi et al 2007, Hanif et al., 2008, Shamim et al., 2008, Ullah et al., 2009, Khan et al., 2011). Moreover, as a further proof-of-concept, I examined the efficiency of these compounds to cause cell growth inhibition and apoptosis in cancer cell lines. It was seen that these compounds are able to significantly inhibit the cancer cell growth and induce apoptosis in different cancer cell lines and that this action can be reversed by the use of copper-specific chelator, neocuproine, whereas other metals chelators do not offer any significant protection. 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. Studies on chemopreventive and therapeutic plant-derived phytonutrients assume significance in view of the fact that such compounds exhibit negligible or low toxicity even at relatively higher concentrations. Further they may also act as lead compounds for the synthesis and development of novel anticancer drugs.