CHAPTER I

INTRODUCTION
The dietary factors can contribute to human cancer risk and as such many of the cancers common in the third world countries and the western world, including liver, colon, prostate and breast cancers have been related to dietary behaviours. Dietary carcinogens identified to date include the mycotoxins, heterocyclic amines formed from the heat treatment of meat, N-nitroso compounds and polycyclic aromatic hydrocarbons. Diet related cancer occur through an imbalance of carcinogenesis and anticarcinogenesis. Dietary anticarcinogens may therefore provide a means of retarding, suppressing or reversing the multi-stage carcinogenesis. An avalanche of dietary and plant-derived compounds has been reported to possess anticarcinogenic activities. The most of these agents possess intrinsic antioxidant, radical trapping and anti-inflammatory properties, which appear to contribute to their chemopreventive properties. Curcumin the natural yellow pigment in turmeric isolated from the rhizome of the plant *Curcuma longa* elicit striking inhibitory effects on diverse cellular events associated with the process of carcinogenesis (Farombi, 2004).

Curcuminoids, a group of phenolic compounds isolated from the roots of *Curcuma longa* (*zingiberaceae*), exhibit a variety of beneficial effects on health and on events that help in preventing certain diseases. A vast majority of these studies were carried out with curcumin (diferuloyl methane), which is a major curcuminoid. The studies using curcumin include anti-inflammatory, antioxidant, anticarcinogenic, antiviral and antiinfectious activities were reported by different authors (Joe et al., 2004).

Several classifications of the mechanisms of anticancer agents have been proposed by a number of investigators. Wattenberg (1985) subdivided anticarcinogens into two major categories, blocking agents and suppressing agents on the basis by which they exert protective effect at specific stages of multi-step carcinogenesis. Blocking agents are substances that can inhibit initiation either by inhibiting the formation of carcinogens from precursor molecules or reactive intermediates from the parent carcinogens, or by
preventing the ultimate electrophilic species from interacting with macromolecules such as DNA, RNA and proteins. Suppressing agents act at the promotion or progression stage by preventing the malignant expression of initiated cells. Some classifications of anticarcinogens distinguish inhibitors based on their intervention level throughout the process leading from a normal cell to an initiated cell, and then to dysplasia of increasing severity up to carcinoma in situ and ultimately to cancer (Kelloff et al., 1994). De Flora (1998) presented a detailed classification of mechanisms of inhibitors of mutagenesis and carcinogenesis.

Curcuma extract can be administered safely to patients at doses up to 2.2 gram daily, equivalent to 180 mg of curcumin. Curcumin has low oral bioavailability in human and may undergo intestinal metabolism and larger clinical trials of curcuma extract are merited (Sharma et al., 2001).

In general terms, three different levels of disease prevention have been identified namely primary prevention, secondary prevention and tertiary prevention. Primary prevention means preventing the occurrence of diseases. Secondary prevention involves early diagnosis and intervention particularly at the preclinical stage with the objective of reversing, inhibiting or delaying the progress of the disease condition. Tertiary prevention deals with the reduction of the impact of the disease via prevention of complication and early deteriorations (Last, 1986).

Chemopreventive activity of curcumin has been indicated when administered before, during and after carcinogenic treatment as well as when administered during the promotion and progression phase of colon carcinogenesis in rats (Kawamori et al., 1999). Thus, it has been shown that curcumin inhibited tumour initiation induced by benzo (a) pyrene and 7,12 dimethyl benz (a) anthracene and tumour promotion induced by phorbol esters (Deshpande and Maru, 1995 ; Huang et al., 1995). Curcumin showed a dose
dependent decrease in cytochrome P 450 and aryl hydrocarbon hydroxylase activity with concomitant decrease in B (a) P - DNA adduct in cells treated with benzo (a) pyrene (Deshpande and Maru, 1995). A similar study also revealed the inhibition of cytochrome P4501A1 activity and formation of carcinogen DNA abducts in 7,12 dimethylbenzanthracene treated human mammary epithelial carcinoma (MCF-7) cells by competitively binding to the aryl hydrocarbon receptor (Ciolino and Yeh, 1998).

Incidence of cancer at different sites may be related to oxidative damage to host genome by genotoxicants. These oxidative actions may be modified by phytochemicals present in foods. The non-nutritive dietary constituents which possess antimutagenic property are reported to be promising chemopreventive agents. Polasa et al. (2004) reported the protective effect of curcumin on B (a) P induced DNA damage in human peripheral blood lymphocyte cells.

The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumour cells, down-regulate transcription factors NF - Kappa B, AP-1 and Egr-I; down-regulate the expression COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2) and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinase. Aggarwal et al. (2003) reported that curcumin could suppress tumour initiation, promotion and metastasis.

Iqbal et al. (2003) reported that dietary antioxidants protect laboratory animals against the induction of tumours by variety of chemical carcinogens. Protection against chemical carcinogenesis could be mediated via antioxidant dependent induction of detoxifying enzymes. Dietary supplementation of curcumin (2%, w/v) to male mice for 30 days significantly increased the activities of glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and catalase to 189%, 179%, 189% and 181% in liver and
143%, 134%, 167% and 115% in kidney respectively as compared with corresponding normal diet fed control.

Free radicals such as superoxide radicals, hydroxyl radicals and hydrogen peroxide which potentially can activate NF-Kappa B. Benzo (a) pyrene, the potent carcinogen that activate NF-Kappa B are either tumour initiators or promoters and NF-Kappa B activation can block apoptosis, promote proliferation and mediate tumorigenesis. The effect of curcumin on carcinogen induced NF-Kappa B activation and NF-Kappa B regulated gene expression in human non-small cell lung carcinoma cells are through suppression of one Kappa B alpha kinase (Shishodia et al., 2003).

Oxidants are toxic, but at low doses they can stimulate rather than inhibit the growth of mammalian cells and play a role in the etiology of cancer and fibrosis. The effect of oxidant on cells is modulated by multiple interacting antioxidant defense systems (Amstrad et al., 1991). The balance of superoxide dismutase and catalase plus glutathione peroxidase is more important for overall sensitivity than the level of Cu, Zn-SOD alone. Growth stimulation may occur when cells are protected from excessive oxidant toxicity but only when a sufficient oxidant signal remains to activate the necessary growth pathways. Oxidants are ubiquitous in our aerobic environment and are formed in-situ in tissues and cells by normal metabolism and the metabolism of certain xenobiotics. They are always toxic and produce macromolecular damage. At the same time oxidants can serve as pathophysiological signals in growth and differentiation (Cerutti, 1985). The sensitivity of cells to oxidants is attenuated by low molecular weight antioxidants and antioxidant enzymes. The biochemistry of the most important enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), GSH reductase, and glutathione - S-transferases has been studied. However, the physiological role of a single antioxidant enzyme in situ in the cell is only poorly understood because of complex interactions and interrelationships between the individual components.
Augmentation of tissue SOD is a useful therapeutic strategy in certain diseases having an oxidative injury component (Ewing and Janero, 1996). The activities of Copper-Zinc superoxide dismutase (Cu, ZnSOD) in biological samples might be used as nonspecific prognostic marker in assessing cellular and mitochondrial tissue destruction (Durak et al., 1996).

Human manganese containing superoxide dismutase (MnSOD), the nuclear encoded mitochondrial protein, scavenges potentially toxic superoxide radicals by dismuting $O_2^-$ to $O_2$ and $H_2O_2$ (Zhang, 1996). Li et al. (1998) suggested that the gene for MnSOD is a candidate tumour suppressor gene and MnSOD over expression may modulate the malignant phenotype.

Curcumin inhibits the generation of reactive oxygen species (ROS) and the c-Jun NH$_2$-terminal kinase (JNK) pathway. It exhibited antioxidant properties and inhibited both JNK activation and mitochondrial release of cytochrome c in a concentration dependent manner. Somasundaram et al. (2002) reported that the dietary supplementation with curcumin significantly inhibit cyclophosphamide induced tumour regression in vivo model of human breast cancer. Curcumin was found to possess chemopreventive effect against skin cancer in mice. Chuang et al. (2000) reported that the effective inhibition of N-diethylNitrosoamine induced hepato carcinogenesis in the mouse by curcumin.

Epidemiological data also suggest that curcumin may be responsible for the lower rate of colorectal cancer. Curcumin is a naturally occurring powerful anti-inflammatory medicine. The anticancer properties of curcumin have been shown in cultured cells and animal studies. Curcumin inhibits lipoxygenase activity and is a specific inhibitor of cyclooxygenase-2 expressions. Curcumin inhibits the initiation of carcinogenesis by inhibiting the cytochrome P-450 enzyme activity and increasing the levels of glutathione-S-transferase. Curcumin inhibits the promotion/progression stages of carcinogenesis. The anti-tumour effect of curcumin has been attributed in part to the arrest of cancer cells in S,
G2/M cell cycle phase and induction of apoptosis. Curcumin inhibits the growth of DNA mismatch repair defective colon cancer cells. Therefore, curcumin may have value as a safe chemotherapeutic agent for the treatment of tumours exhibiting DNA mismatch repair deficient and micro satellite instable phenotype. Curcumin should be considered as a safe, non-toxic and easy to use chemotherapeutic agent for colorectal cancers arise in the setting of chromosomal instability as well as micro satellite instability (Chauhan, 2002).

Analysis of curcumin structure revealed the presence of beta-diketone moiety and phenolic hydroxy groups that were suggested to contribute to antioxidation. And vanillin, ferulic acid and a dimer of curcumin were identified as the curcumin-derived radical reaction products. To dissect its anticarcinogenic mechanisms a number of curcumin targets were identified including the aryl hydrocarbon receptor, cytochrome P450, glutathione S-transferase, serine/threonine kinases, transcription factors, cyclooxygenase, ornithine decarboxylase, nitric oxide synthase, matrix metalloproteinases and tyrosine kinases (Leu and Maa, 2002). Kouri et al. (1982) however reported that there is no relationship between AHH/Cytochrome c activity and family history of cancer, location or historical type tumour.

To select the best chemopreventive drug candidates for clinical trial and the necessity to monitor efficacy in the short and intermediate term, render the identification of specific mechanism based in vivo markers of biological activity, a high priority. Antioxidation inhibition of arachidonic acid metabolism, modulation of cellular signal transduction pathways, inhibition of hormone and growth factor activity and inhibition of oncogene activity are reported as mechanisms by which the curry ingredient curcumin exert tumour suppression (Gescher et al., 1998). A better understanding of these mechanisms helps the establishment of screens for the discovery of new and better chemopreventive agents and the identification of surrogate markers to assess the outcome of clinical chemoprevention trials.
Simultaneous treatment of turmeric with lead acetate significantly reduces the genotoxicity induced by lead administration and the powerful protection was reported with 5% powdered turmeric. Turmeric is useful herbal remedy specially for controlling oxidative damages and genotoxicity induced by lead acetate intoxication (Ibrahim et al., 2006).

Singh and Khar (2006) reported that cell lines that are resistant to certain apoptotic inducers and radiation become susceptible to apoptosis when treated in conjunction with curcumin. It acts as a chemopreventive agent in cancers of colon, stomach and skins by suppressing; colonic aberrant crypt foci formation and DNA adduct formation.

Curcumin also reduced the levels of nitric oxide (NO) and O$_2$ associated with the favourable expression of Th1 and Th2 cytokines and inducible NO synthase. Consistent in colonic mucosa was suppressed in the curcumin treated mice. These findings suggested that curcumin or diferuloylmethane, a major component of the food flavour turmeric, exerts beneficial effects in experimental colitis and may, therefore, be useful in the treatment of inflammatory bowel disease (Ukil et al., 2003).

Curcumin was found to inhibit the generation of ROS including super oxide dismutase and hydrogen peroxide in peritoneal macrophages (Joe and Lokesh, 1994). It inhibits lipopolysaccharides and interferon-g-induced production of nitric oxide in macrophages (Brouet and Oshima, 1994) and inhibition of inducible nitric oxide synthase gene expression in isolated BALB/c mouse peritoneal macrophages (Chan et al., 1998). It exhibits an anti clastogenic (Araujo and Leon, 2001), anti fungal (Bartine and Tanaoui – Elaraki, 1997) and anti-viral properties (Barthelemy et al., 1998).

Curcumin has been shown to prevent cancer in the skin, forestomach, duodenum and colon of mice and in the tongue, colon, mammary glands and
sebaceous glands of rats. Of particular interest is the ability of dietary curcumin to interfere with colon carcinogenesis in chemicals and genetic rodent models (Rao et al., 1995). Curcumin has also been associated with regression of established malignancy in humans (Kuttan et al., 1987). Curcumin is the major constituent of the spice turmeric, which is abundantly used in the diet on the Indian subcontinent, an area that has a low incidence of colorectal cancer (Greenlee et al., 2000). Mechanisms by which curcumin prevents cancer are thought to involve up regulation of carcinogens detoxifying enzymes such as GST s3 (Piper et al., 1998), antioxidation (Subramanium et al., 1994), and suppression of expression of enzyme cyclooxygenase-2 (Ireson et al., 2001). The pharmacokinetic properties of curcumin in human remain unexplored. In rodents, curcumin undergoes avid metabolism by conjugation and reduction and its disposition after oral dosing is characterized by poor systemic bioavailability (Wahlstrom and Blennow, 1978). In view of the paucity of pharmacodynamic and pharmacokinetic information regarding curcumin in human, we conducted a dose escalation pilot study of a standardized \textit{Curcuma} extract in patients with advanced colorectal cancer refractory to standard chemotherapy. Malondialdehyde is a naturally occurring product of lipid peroxidation and prostaglandin biosynthesis via cyclooxygenase (Marnett et al., 1999). These two cellular processes implicated in the pathogenesis of colorectal cancer are inhibited by curcumin in preclinical models (Taketo et al., 1998; Venkatesan et al., 2000). In a recent study in rats, dietary curcumin was shown to up-regulate GST activity in the liver and diminish M1G levels in colon mucosa and these effects were accompanied by measurable tissue levels of curcumin (Sharma, 1976).

Soni and Kutton (1992) reported a protective effect of curcumin on aflatoxin induced hepatic preneoplastic focus formation in rats, shedding light on the feasibility of using curcumin in the prevention of human hepato carcinogenesis. Curcumin effectively inhibits DEN-induced HCC formation in the mouse. Alterations in the levels of several representative cellular markers,
including P21ras, PCNA and CDC2, indicate the beneficial biological effect of curcumin. P21ras is a proto-oncogene activated during carcinogenesis in various organs, especially in the lung and colon (Hendrickse et al., 1994). PCNA is a biomarker of cell proliferation (Habig et al., 1974). Increased levels were observed in both preneoplastic and tumour cells. CDC2 (De Sousa et al., 1998) is required in normal progression through the G2/M phase of the cell cycle. Decreased expression of these proteins indicates growth inhibition and may lead to cell cycle arrest or apoptosis, which in turn may attenuate the development of cancer. These curcumin induced cellular changes were in accord with the criteria for an effective chemopreventive agent. It seems that curcumin differentially, and may be beneficially, inhibits only those targets that should elevated levels in HCC, such as P21ras, PCNA and CDC2, but not those that do not show differences in tumor tissues, such as CDK2. Although CDC2 (G2/M transition) and CDK2 (G1/S transition) are both crucial in cell cycle progression, their role in hepatocarcinogenesis and response to curcumin intervention are apparently different. Many other cellular targets of curcumin have been reported, for example, the inflammatory reaction (Harries et al., 1997), AP-1, PKC, on rushing decarboxylase, lipoygenase, cyclooygenase, free radical scavenging activity (Sevilla et al., 1997); i-NOS, tumour necrosis factor-α and nuclear factor KB, the cellular detoxification system (Satoskar et al., 1986) and the apoptosis related machinery (Sambaiah et al., 1982).

The specific activity of aryl hydrocarbon hydroxylase in mammary gland cancer susceptibility and resistance under basal condition and after pretreatment of mice with 3 MC was studied by Chuang and Bresnick (1976). Aryl hydrocarbon hydroxylase (AHH), a drug metabolism enzyme is useful in determining the individual differences in genetic susceptibility to lung carcinogenesis. AHH is a microsomal membrane bound monooxygenase system located in most tissues of the body. In mice, AHH inducibility is under the control of Ah locus and certain inbred strains of mice are susceptible to AHH induction by 3 methylcholanthrene treatment (Ah responsive strains), while other strains are not (Ah non-responsive
strains). A strong correlation was observed between AHH inducibility and tumour incidence in mice (Kiyohara and Hirohata, 1994). Kellermann et al. (1973) investigated the genetics of AHH in human population and reported that the inducibility of AHH enzyme was controlled by a single gene locus with 2 dominant alleles. They classified human as having low, intermediate, or high inducibility of AHH. In addition, they reported a significant positive correlation between the extent of inducibility and susceptibility to lung cancer. A close association between development of lung cancer and three polymorphisms of CYP1A1 caused by the presence or absence of one MspI site in the 3'-flaking region, namely a predominant homozygote pattern (A), a heterozygote pattern (B) and a homozygous rare allele pattern (C), has been reported. The relationship between AHH inducibility and polymorphisms of CYP1A1 had not been investigated previously.

Induced aryl hydrocarbon hydroxylase was expressed in 4 out of 12 primary and 12 out of 19 secondary hybrid clones examined. Constitutive hydroxylase activity was detectable in 9 of the 15 inducible clones. The entire hybrid clones that exhibited constitutive hydroxylase activities were also inducible. There was a positive correlation between constitutive and induced hydroxylase activities although the absolute levels of enzyme showed a wide range between different clones. Isoenzyme analysis performed on 12 primary and 19 secondary hybrid clones showed that aryl hydrocarbon hydroxylase activity was concordant with the expression of the human isoenzymes malate dehydrogenase (EC 1.1.1.37) and isocitrate dehydrogenase (EC 1.1.42), previously assigned to human chromosome 2. Isozyme markers for 19 other human chromosomes segregated independently from aryl hydrocarbon hydroxylase activity. The results suggest that the gene(s) required for aryl hydrocarbon hydroxylase activity are located on human chromosome 2 (Brown et al., 1976).
Active oxygen species can play a role in the pathogenesis of the polyp-adenoma-carcinoma sequence of colon carcinoma where some defensive role of antioxidant enzymes has been suggested (Staruchov et al., 1995). MnSOD level of cancer cells is an important prognostic factor in radiation therapy for cervical cancer (Nakano et al., 1996).

During the past few years antioxidant activity in tumour cells has received enormous attention (Gerber et al., 1991; Malvy et al., 1993). The role of antioxidant impairing in experimental cancer is of utmost importance (Shamberger et al., 1973). The neoplasm of cells are dependent on high metabolic activities which may lead to the generation of immense quantity of free radicals. Investigators of biochemistry and medicine have been aware of the antioxidant imbalances in carcinogenesis because these imbalances are being considered in connection with the production and treatment of cancer.

'Cancer' is an imprecise descriptive term to cover all the conditions in which cell proliferates for whatever the reason in a more or less uncontrolled manner, invade tissues and set up satellite growth in other organs. The overall result of such a process, if left undisturbed, is always the death of the host (Faber, 1973).

The malignant transformation is the result of two stages i.e. the stage of initiation and the stage of development into malignant cells (Pitol and Heidelberger, 1963). Carcinogen triggers initiation either by deletion or by inactivation of enzymes involved in the regulation of oxidative or synthetic pattern of the cells. However, Faber (1973) advocated a possibility of a process of initiation followed by subsequent steps concerned with stimulation of growth for development of cancer. Polycyclic aromatic hydrocarbons (PAH) are compounds formed during incomplete combustion of organic matter (Goldman and Shields, 2003). Methylcholanthrene is a major carcinogenic compound of these groups. The target organs for PAH are the lung, breast, oropharynx, genitourinary and
gastrointestinal tracts. (Goldman and Shields, 2003). In rodents, diets with PAH have been reported consistently induce cancer of the foregut and lung tumours (Singh et al., 1998).

Many carcinomas are diagnosed and thought to be related with the inefficiency of the antioxidant system caused by the malignant tissue, which has lost some of its more specialized metabolic reaction steps resulting in an oxidative stress. The effect of varying levels of antioxidants is normal as well as in different tumours forms the basis of much experimental work in laboratory animals. It is however difficult to collect such information in human and reliable results can be obtained only from detailed case reports of abnormalities of antioxidants, correlated with the subsequent establishment of cancerous growth.

The close relationship between tumour growth and free radical generation has led to the working hypothesis that an endogenous impairment of different antioxidants may be responsible for the initiation and maintenance of tumour growth (Mulder et al., 1995). This concept has provided the stimulus for much work in recent years. The key to the puzzle of free radicals in cancer was the isolation of different antioxidants (Durak et al., 1996).

This cellular defense system is constituted by antioxidant enzymes like superoxide dismutase, glutathione peroxidase and catalase as well as hydrophilic antioxidants such as ascorbate, reduced glutathione, urate etc. and lipophilic antioxidants like tocopherols, carotenoids and phylloquinone.

Three groups of antioxidants make up the antioxidant system viz.

1. Primary antioxidant
2. Secondary antioxidant
3. Tertiary antioxidant.
As studies reveal the depth of the oxidant's destructive potential, investigators have been studying various ways – both normal and synthetic, to diffuse free radicals in the hope of reversing or halting the progress of many diseases they are believed to cause or promote.

High intake of certain antioxidants has been associated with a reduced risk of cancer (Block, 1992). The inhibitory action of retinoic acid on cervical carcinogenesis in mouse is reported by Manoharan and Rao (1984). Dorgan and Schatzkin (1991) studied antioxidant micronutrients in cancer prevention and put forwarded the idea that though these antioxidants such as carotenoids, vitamin E and vitamin C play a protective role in cancer of animals yet there role in cancer prevention in human is less clear. There is no convincing evidence about the effect of endogenous antioxidants in the process of carcinogenesis, however the role of carotenoids, tocopherols, vitamin C and vitamin K in certain neoplasm have been reported by many investigators in different times (Garland et al., 1993).

The determination of the blood levels of different antioxidants and the estimation of the relative amounts thereof, may demonstrate interesting empirical relationship to various types of neoplastic diseases (Oberley and Buttner, 1979; Gonzales et al., 1984). In healthy organism a characteristic equilibrium exists between the occurrence of highly reactive oxygen species and their destruction by antioxidants.

Among the targets of oxidative attack phospholipids containing unsaturated fatty acyl moieties are of utmost importance in recent researches. One major feature of oxygen metabolism is its interaction with polyunsaturated fatty acids or derived free radicals resulting lipid peroxidation of the biological membranes leading to gross disturbances in structural organization and in associated enzymic function (Slater, 1972). Lipid peroxidation in vivo or in vitro produces irreversible damage to membrane systems, which often results in the
death of the affected cells. The potential effects of malondialdehyde (MDA), the membrane derived carboxyl end product of lipid peroxidation, on nuclear material was suggested by Goldstein (1976). Lipid peroxidation causes cancer and diet rich in polyunsaturated fatty acid leads to an increased incidence of cancer. Malondialdehyde has been reported to be tumour initiator in a mouse skin carcinogenesis system (Shamberger et al., 1974). The MDA is suggested to be higher in carcinomatous tissue than in non-diseased organ (Bauer and Wendel, 1980; Capel and Thornby, 1982). Troll et al. (1978) observed that in laboratory rodents, which were fed dies containing both 4% and 15% fat either predominantly saturated or unsaturated, the tumour incidence was significantly higher in the groups fed on unsaturated rather than saturated fat. The unsaturated fat enhancement of tumour yield has been similar with both dimethylbenzanthracene and b-propiolactone in initiation of neoplasia, which is independent of altered microsomal metabolism (Goldstein, 1976).

The exploration of lipid peroxides with antioxidant profile in blood with various tumours as well as in experimental carcinogenesis has provided many important links in relating the oxidant and antioxidant reactions (Barclay and Vinquist, 1979; Apaja, 1980; Gorozhanskaia et al., 1995).

The measurement of primary antioxidant enzyme profile including superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), which has been investigated by a number of investigators, has not seen to be so useful in recognizing or in diagnosis of the disease (Guner et al., 1996). The reported results with a more sophisticated approach to this area will definitely establish the relationship among cancer and antioxidants. However, the puzzle among chemical carcinogenesis, oxidative attack, antioxidant profile and the inhibitory role of chemopreventive agents as curcumin still remains unrevealed. Therefore, in the light of foregoing information and ideas an investigation is aimed to study the “Effect of curcumin on primary antioxidant status and mixed
function oxygenase enzyme system during cholanthrene induced carcinogenesis" in the following plan:

1. To study the effect of curcumin on changes in primary antioxidant enzymes in albino mice at a regular interval of time during 3-methyl cholanthrene induced carcinogenesis and correlating the results with those of normal animals and 3-methylcholanthrene treated animals.

2. To observe the changes in mixed function oxygenase enzymes consisting of aryl hydrocarbon hydroxylase, cytochrome P450 and xanthine oxidase in liver, kidney and stomach tissue of albino mice at a regular interval of time with the simultaneous supplementation of curcumin and 3-methylcholanthrene and correlating the results with those of normal and 3-methylcholanthrene treated alone.

3. To study the effect of curcumin on changes in blood and tissue lipid peroxide content in albino mice at a regular interval of time during 3-methylcholanthrene induced carcinogenesis.

4. To study the effect of curcumin on changes in alpha-fetoprotein as cancer marker in albino mice during 3-methylcholanthrene induced carcinogenesis at regular time interval and to correlate the findings with those of normal and lone 3-methylcholanthrene treated animals.


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