Introduction
"From the right to know and the duty to inquire flows the obligation to act."

Cancer is a complex group of diseases, results partly from changes in genes that control cell growth and behavior and partly from interactions between these genetic changes and the cellular stresses from specific environmental and behavioral factors, including lifestyle choices (Perera 1996). Following heart diseases, cancer is second leading cause of death in developed parts of world and the third leading cause of death in developing countries after heart and infectious diseases. It is estimated that about 70% of all cancer deaths occur in countries having limited or nonexistent resources available for prevention, diagnosis and treatments (Jemal et al., 2007). Each year 10.9 million people worldwide are diagnosed with cancer and there are 6.7 million deaths from the disease. It is estimated that there are 24.6 million people alive who have received a diagnosis of cancer in the last five years (Jemal et al., 2007). Despite many therapeutic advances, overall mortality statistics are unlikely to change until there is a reorientation of the concepts for the use of natural products as new chemotherapeutic agents (Anand et al., 2008). Since ages natural or semi-synthetic compounds are widely used to cure various diseases. Around the globe researchers have now shifted their focus to check or prevent the cancers development using natural compounds.
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The transformation of a normal cell into a cancerous one proceeds through three main stages over a number of years or even decades (Couch 1996). The process of carcinogenesis includes initiation, promotion, and progression stages (Fig. 1). In brief, initiation stage involves an interaction between the cancer causing substances referred to as carcinogen and the DNA of the cells. This is followed by the promotion stage which occurs very slowly, period ranging from several months to years. During this stage, a change in diet and lifestyle can have a beneficial effect so that the person may not develop cancer during lifetime. The stage of promotion is partially reversible thus the most effective site to target for both active and passive cancer prevention strategies. The final stage i.e. progression involves progression and spread of the cancer at which point, diet may have less of an impact. Therefore, preventing initiation of carcinogenesis is an important anticancer strategy which provides an opportunity to inhibit cells becoming malignant. Hence, the knowledge of the genetic hallmarks of carcinogenesis provides an opportunity to use approaches such as dietary intervention to prevent cancer development.

Causative factors:

Among the major causes of cancer development both external (environment and life-style habits) and internal (individual's genetic makeup, inherited mutations, immune conditions etc.) factors are involved. These causal factors may act together or in sequence to initiate or promote carcinogenesis. Indeed, it is
Fig. 1. Schematic representation of stages of carcinogenesis
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estimated that up to 80 to 90% of all cancers are attributable to environmental risk factors (Mucci et al., 2001).

A normal cell transforms into a malignant one because it loses the growth control by deregulation of cell signals followed by alterations in gene regulation brought about by changes either in the regulatory region or in proteins involved with coordinated cellular functions (Carbone and Pass 2004). Majority of the environmental mutagens and/or carcinogens have multiple cellular target(s) to exert their effects. They can induce genomic changes by targeting DNA directly and/or indirectly and/or by binding to proteins involved in the maintenance of genome integrity e.g. tubulins, DNA repair enzymes, proteins involved in the control of cell cycle etc. (Nohmi et al., 2005). Since, mutations which are induced via carcinogen-DNA adducts formation, should correlate with the DNA-binding characteristics of the carcinogen. This is the initiation of mutation or mutagenesis, and without proper execution of DNA repair (DNA repair happens naturally under normal circumstances), the cell propensities towards carcinogenesis.

Apart from exposure to carcinogens other factors such as, the genetic predisposition of an individual have also been well documented for the development of cancer. Patients with the genetic xeroderma pigmentosum are more susceptible to skin cancer (Yarosh et al., 2001) and incidence of bladder cancer is significantly higher in those individuals who have the slow acetylator phenotype, especially if they are exposed to aromatic amines (Cui et al., 2001).
Cancer Chemoprevention: An Insight

Nowadays the aspect 'chemopreventive' has been largely associated to a individual's proper lifestyle, including healthy diet. The time worn adage, "an ounce of prevention is worth a pound of cure,". Michael Sporn, (1976), coined for the term 'chemoprevention', referring to the activity of natural forms of vitamin A in preventing the development and progression of epithelial cancer, thus originated a novel field in cancer research. Cancer chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage or by arresting or reversing the progression of premalignant cells in which such damage has occurred (Sporn 1976). Later on, Sporn and Suh (2002) redefined the term cancer chemoprevention, according to them, 'use of natural or pharmacological agents to suppress, arrest or reverse carcinogenesis, at its early stages. Till date, 'cancer chemoprevention' passed more than 6800 citations in the last quinquennium and now broadly used to indicate the ability of a molecule not only to prevent, but also to cure cancer. Recent researches around the globe involving data from epidemiological studies; clinical trials on patients; studies on animal models where carcinogenesis was experimentally induced and in vitro tests on cell lines provide evidences on the efficacy of 'chemopreventive' approaches in cancer.

Model Systems for Cancer chemoprevention studies

The phenotype of a cell is determined by the environment and its genetic makeup, therefore the milieu in an intact organism is required to test the
relevance of any proposed mechanism to cancer chemoprevention. Very few of the many systems used in experimental studies on cancer chemoprevention *in vivo* and *in vitro* have evolved to the point where a stepwise analysis seems feasible. In these systems, some patterns of cancer chemoprevention do mimic to varying degrees to human situations. Especially for the skin cancer, such chemoprevention assays could be an important armamentarium because of increasing incidence of such cancers in western population. As skin is continuously exposed to a variety of environmental carcinogens that include both chemical agents and ultraviolet radiations; it is one of the most suited experimental models for studying any chemopreventive regime. A wide range of compounds, both synthetic and naturally occurring has been earlier screened for their cancer chemopreventive effects in skin carcinogenesis models (Gupta and Mukhtar 2002).

**Cancer Chemopreventive Agents**

On the basis of mechanism of action, chemopreventive agents are divided into 2 broad categories, namely *blocking agents* and *suppressing agents* (Wattenberg 1985). Blocking agents prevent carcinogens from reaching the target sites (initiation), from undergoing metabolic activation or from subsequently interacting with cellular macromolecules DNA, RNA and proteins. Thus preventing carcinogens to hit their cellular targets by enhancing carcinogen detoxification, modifying carcinogen uptake and metabolism, scavenging reactive oxygen species and enhancing DNA repair. Suppressing agents inhibit the
malignant transformation of initiated cells at either the promotion or progression stage of carcinogenesis and can also retard the development of precancerous cells into malignant ones by interfering through regulation of cell cycle, signal transduction, transcriptional regulation and induction of apoptosis (Greenwald 2004; Surh 2003). Many researchers showed that the molecular events those are affected or regulated by the phytochemicals include carcinogen activation/detoxification by xenobiotic metabolizing enzymes; DNA repair; cell-cycle progression; cell proliferation, differentiation and apoptosis; expression and functional activation of oncogenes or tumor-suppressor genes; angiogenesis and metastasis; and hormonal and growth-factor activity etc. (Surh 2003). Therefore, the ability of any cancer chemopreventive agent to prevent or retard the tumor development can be recognized and assessed on the basis of combination of several distinct sets of events at its intracellular levels, rather than a single biological response exerted by same (Gescher et al., 1998).

Phytochemicals and Cancer Chemoprevention

Phytochemicals, the non-nutrient substances present in plant food, are associated with certain health benefits together with those associated with reduced risk of cancers (Russo 2007). They may potentially act as an antioxidant, affect hormone metabolism, stimulate enzyme activity and prevent harmful DNA replication (Surh 1999). Although current therapeutic advances in cancer treatment have evidently given good results but, unfortunately accompanied by many undesired side-effects. However, many researches
evidently revealed that the phytochemicals, beside their effectiveness in the
treatment of milieu of diseases, are also non-toxic and without undesired side-
effects too. This opened an avenue for the field cancer chemoprevention through
phytochemicals. Dietary agents consist of a wide variety of phytochemicals that
are ubiquitous in plants and many of them have been used as safe traditional
medicines for human beings since years (Aggarwal and Shishodia, 2006). Research findings supporting the use of phytochemicals in cancer
chemoprevention are well documented by systematic strategy that begins from
surveying the results of epidemiological, laboratory, and clinical research. As a
result, many natural compounds, belonging to diverse structural and functional
chemical classes, have been identified as potent cancer chemopreventive agents
including curcumin, genistein, indole-3-carbinol, resveratrol, diallyl sulphide, [6]-
gingerol, lupeol, bromelain, etc.. These phytochemicals reduces cancer risk
through a number of mechanisms and prevent carcinogenicity at different stages
(Kelloff et al., 1999; Nishino et al., 2007).

Scientists typically categorize phytochemicals into classes based on their similar
chemical structures. Briefly, phytochemicals include: phenols- comprising
flavonoids (e.g. resveratrol, catechins, anthocyanins and isoflavones, phenolic
acids and lignans); terpenes- comprising carotenoids (e.g. beta-carotene,
lycopene and lutein, monoterpenes and saponins) and thiols- also known as
organosulfur compounds, including indoles and isothiocyanates (e.g. allyl
sulphide; diallyl sulphide; indole-3-carbinol).
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Phenolic substances, present in dietary and medicinal plants, have been reported to possess substantial anti-carcinogenic, antioxidative, anti-inflammatory and antimutagenic activities. For example: capsaicin, a pungent ingredient of hot chili pepper; curcumin, a yellow ingredient from turmeric; resveratrol, a phytoalexin found in grapes and (-)-epigallocatechin gallate, a major green tea polyphenol, are well reported for anti-mutagenesis and anti-tumorigenesis potential in in vivo and in vitro studies. Among these, another promising plant phenolic phytochemical is [6]-gingerol, oleoresin from rhizomes of ginger (Zingiber officinale Roscoe, Zingiberaceae). [6]-gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone) and its homologs have been found to possess many pharmacological properties, such as anti-inflammatory, analgesic, antipyretic, antihepatotoxic, cardiotoxic effects as well as anti-tumor and anti-proliferative effects (Mustafa et al., 1993; Mascolo et al., 1989).

Though the literature supports the role of [6]-gingerol as a potential cancer chemopreventive agent, still its mechanism of action is largely unknown. Thus the present piece of work is dedicated to explore the mechanism of action of [6]-gingerol in in vitro and in vivo skin cancer models with the following objectives:

- To analyze the antimutagenic potential of [6]-Gingerol against carcinogen induced DNA damage.
- To investigate the influence of [6]-Gingerol on cell cycle regulation.
- To study apoptosis as a mechanism of cancer chemoprevention by [6]-Gingerol.
- To quantify the amount of [6]-gingerol in locally available ginger rhizomes.