Introduction
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Cancer is a disease of multicellular organisms in which organismal control of cell division is lost in the affected cells and the cells start proliferating uncontrollably. This may lead to the development of malignant tumors that eventually cause the death of the individual. The development of cancer or the process of carcinogenesis is a multifactorial, multiphasic and multigenic phenomenon. The earliest records of cancer in man were found in the collections of medical and surgical observations assembled in Egypt around 1500 B.C that are known as Elber's Papyrus. By about the fourth century B.C, Hippocrates assigned the name 'cancer' to the maladies displaying morphologically a crab like appearance found in the breast, uterus and stomach.

Cancer may be caused by physical, viral or chemical agents. Epidemiological studies have established associations between a number of environmental factors and the incidences of different types of cancers. Some associations are very strong, like tobacco consumption and oral cancer. From these studies, it is inferred that many types of cancers are potentially preventable. Most of the carcinogenic agents cause alteration/damage to DNA affecting the expression of proto-oncogenes and tumor suppressor genes and finally leading to neoplastic transformation of the cell.

Ionizing radiations viz. electromagnetic (x-rays and γ-rays) or particulate radiation (electrons, protons, α-particles or other charged heavy particles), ultraviolet radiation etc. possess the ability to induce cancer. UV-radiations are capable of inducing skin tumor as their penetration is skin deep. Ionizing radiations can induce tumors in any tissue of the body as these penetrate deeper, and they are known to be highly effective in producing deletions, chromosome translocations and as well as point mutations, which may eventually lead to the activation of proto-oncogenes and suppression of tumor suppressor genes. Electro-magnetic field exposures have also been implicated for their carcinogenic action (Tannock and Hill, 1988).

Among the biological factors that cause cancer, viral etiology is of great importance. Both oncogenic RNA viruses and oncogenic DNA viruses are known to cause cancer. The papova viruses, adeno viruses, hepatitis viruses and herpes viruses are oncodnaviruses while the retroviruses (Type A, B, C and D) are the oncornaviruses.
Epstein-Barr viruses (EBV), herpes simplex-2 (HSV-2), human papilloma viruses (HPV), simian viruses (SV-40), hepatitis B viruses (HBV), cytomegaloviruses (CMV) and human T-cell leukemia viruses (HTLV -I and II) are known to cause cancer cell transformation in human tissues. Human immunodeficiency virus (HIV) is known to produce Kaposi’s sarcoma (Pitot, 1986).

The mechanism of action of different carcinogens may be different. This includes direct interaction of carcinogen with DNA viz. carcinogens like alkylating agents, acylating agents and epoxides. Some compounds which are known as procarcinogens (e.g. polycyclic aromatic hydrocarbon, N-nitrosoamine, aflatoxin, vinyl chloride, etc.) need to be metabolically activated before these begin interacting with DNA and manifesting their carcinogenic effect. At other extremes are some compounds viz. metal ions, fluorouracil, etc. which interfere with DNA replication thereby increasing the mismatching of nucleotides or disturb the nucleotide pool, thus leading to mutational and related events which ultimately trigger to cancerous development.

Cancer chemoprevention

Recent evidences lead credence to 'chemoprevention' i.e. preventing the occurance of cancer as a new phase of meaningful strategy to prevent cancer in human beings. In a developing country like India, primary prevention by inexpensive, practical and effective means should be considered a priority in cancer control in view of limited resources available for diagnosis, not to speak of treatment. ICMR established population based six hospital registers functioning in the country that have provided an estimate of 6,50,000 new cancer cases per year. ‘Cancer chemoprevention’ a term coined by Sporn et al., (1977), is defined as a strategy for cancer which begins with normal appearing tissues and progress from clonal expansion through invasion to eventual metastasis. Currently, this strategy encompasses targeted populations, such as individuals exposed to carcinogenic risk due to their life style (e.g., smokers and snuff chewers); individuals exposed to carcinogenic risk through the media of their occupation (e.g., asbestos workers); those known to be genetically predisposed to the development of cancer (e.g., individuals with familial colonic polyposis); individuals with lesions that are premalignant or preneoplastic (e.g., oral leukopenia in snuff users); survivors of primary cancers with high degree of
recurrence or high tendency towards formation of second primary tumor; and lastly but not the least, cancer survivors who received chemotherapy and/or radiation therapy. Several thousand chemical agents and a large number of defined and undefined mixtures of chemicals have been reported, which either have epidemiological evidence of preventing cancer or exhibit activities either in vivo or in vitro that are mechanistically related to cancer prevention (Kelloff et al., 1997). Ideally, such agent(s) should be free and/or with little or no untoward or toxic effects, should have high efficacy and orally administrable; the latter allows self medication and enhances subject compliance. Only certain high risk populations (e.g., survivors of a primary tumor) can be reasonably expected to endure mild toxicity or discomfort in the use of a chemopreventive agent. Moreover, knowledge of the precise mechanism of action of any prospective chemopreventive agent will decrease the possibility of untoward interactions with other administered drugs or dietary constituents. Furthermore, from economic viewpoint it is understood that the cost of a given chemopreventive regime should be low, since the agent will have to be chronically administered. An understanding of the mechanism of carcinogenesis process is essential for designing the blueprint of any cancer chemoprevention strategy (Figure I).

Most cancer prevention research is based on the concept of multistage carcinogenesis - initiation - promotion - progression. Initiation is considered to occur in one or a few cells of tissue and provoked by metabolic activation of procarcinogen by phase I enzymes such as cytochrome P450 dependent mixed function oxidases which catalyze oxidation, hydroxylation, reduction and hydrolysis. These enzymes can convert procarcinogen into ultimate carcinogen most of which are reactive electrophiles. The multistep activation process of procarcinogens by phase I enzymes is however inhibited by phase II enzymes such as UDP-glucuronyl transferase, sulfotransferases and glutathione S-transferase which primarily facilitates destruction of reactive electrophiles and oxidants into innocuous, excretable metabolites (Puglia and Powell, 1992). The activated electrophiles that are not detoxified by phase II enzymes can interact with and bind to cellular DNA (i.e. DNA adduct) to trigger gene mutations. DNA adducts represent an early, detectable and critical step in the carcinogenic process and thus may serve as an internal dosimeter of carcinogen exposure. Liver is the principle organ involved in the biotransformation of exogenous substances with its capacity to convert hydrophobic
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substances into water soluble products that can be excreted readily from the body. Liver also receives large amounts of nutrients and noxious compounds entering the body through the digestive tract and portal vein. Apart from liver, other extrahepatic organs also have the capacity to detoxify xenobiotics, but their magnitude of induction is less to hepatic tissue. Furthermore, a growing body of evidences have also implicated oxidative stress, a consequence of normal metabolic function, that produces oxygen radical as an important pathogenic factor in development of many human diseases including cancer. Oxidative stress is suggested to be a biologically important factor during progression stage, and enzymes particularly those involved in oxidative stress (such as superoxide dismutase, catalase, glutathione peroxidase, reduced glutathione and lipid peroxidation) be scrutinized for their cancer preventive efficacy and/or degradative pathway. It is thus imperative to evaluate in the host hepatic and extrahepatic organs, the status of phase I, phase II and antioxidant enzymes to delineate the risk of developing cancer.

Approaches to the prevention of cancer are different. Traditionally the most common method has been health education on an individual or a community basis via the mass media or through other channels. The other means are the legislative actions (such as the banning of advertisements), price regulations and policy decisions in relation to health services. A reduction in tobacco use has been one of the principle objectives in most such actions. Now chemoprevention has received growing consideration as a means of cancer control. The development of dietary policies and advice, the elimination or reduction of exposure to chemical carcinogens from the working and the general environment, and the improvement of radiation protection reduce the risk of cancer.

Recently, there has been considerable interest in chemopreventive control of cancer. Chemoprevention requires intervention with vitamins, minerals or other chemicals with the aim of preventing cancer, or more broadly to reverse, suppress or prevent the process of carcinogenesis. World wide there is a large consumption of chemopreventive agents, namely vitamins and minerals, but the scientific evidence of their effectiveness is limited. In many countries primary prevention is multifactorial. Tobacco related legislation, price policy and food additives are examples of intervention in terms of regulative actions. Health education against smoking and to improve diet is also common (Doll, 1990).
Most convincing evidence on the preventability of cancer is provided by many randomized preventive trials. There are considerable epidemiological evidences which showed that effect of environmental factors including personal habits are related with the risk of cancer. The agents commonly used in the chemopreventive intervention are β-carotene, synthetic retinoids, calcium, several vitamins and minerals. The target primary sites are more widespread in the vitamin trials. Tamoxifen is another chemopreventive agent which influence the hormonal balance to prevent breast cancer (Cuzick, 1996). Aspirin trials for cardiovascular diseases as the end point have been provided some insight into the prevention of colorectal carcinomas (Gann et al., 1993). Reduction in the occurrence of invasive primary cancers is the most convincing evidence of the effectiveness of prevention.

The results of the first large intervention studies were published from the α-tocopherol, β-carotene lung cancer intervention trial (ATBC study) carried out in Finland by the National Public Health Institute. There was no protective effect of α-tocopherol or β-carotene on lung cancer or total cancer (Hennekens et al., 1996; Huttunen, 1996; Omenn et al., 1996). Most of the chemopreventive trials are ongoing, but some of the larger trials were stopped before the planned closing date because interim analyses indicated either adverse or no effect (Stewart et al., 1996). However, antioxidants used for chemoprevention presumably act to reduce DNA damage/mutagenesis relatively early in the process of carcinogenesis and are likely to mitigate the risk of cancer.

**Traditional medicinal plants and human health**

The roots of man-plant interaction can be traced back to the early paleolithic period when man learnt, by trial and error, which plant to eat and which to avoid. Later, a systemic approach to ethnomedicine based on observation, experimentation and rational deduction has been developed in different parts of the world. It leads to the establishment of a number of systems like the traditional Chinese system of medicine, Indian Ayurveda, Unani system and the ancient system of Greek medicine.

These man-plant relationships are dynamic and get modified with the flux of time. Intensive studies of tribal plant use have revealed that a number of plants used by them for
medicinal purposes and various other uses, have become endangered due to over exploitation as well as habitat destruction of these plants. Some endangered plant species of traditional medicinal importance in India are *Rauvolfia serpentiana*, *Saussurea lappa*, *Dendrobium pauciflorium*, *Diplomeris hirsuta* etc.

Nowadays the tribal culture is being modified rapidly due to influx of non-tribals in their areas which is reflected through changes in their religious and ethnomedicinal ideas and way of life. It is therefore, not only important to conduct surveys in various areas and observe the ethnic uses of plants by the tribals of the region but it also becomes necessary to repeat studies after a time gap and record the cultural shift. We did ethnomedicinal survey of Madhya Pradesh which is very rich and diverse in flora as well as tribal population. Some of the important surveyed plants have been listed in Appendix I. It was noted that most of these plants are also distributed in other regions of the country.

The use of terrestrial plants for chemoprophylaxis is being practiced by cultures all over the world. In India, a therapy called Ayurvedic medicine and traditional Chinese medicine make use of plant parts and their products as central dogma of the medical system. The very philosophy of Ayurveda revolves around 'prevention'. However, irrespective of the validity of these methods, roughly 79% of world's population and approximately 600 million people in India rely on traditional folklore medicine to some extent. Undoubtedly, natural products represent a rich and untapped resource for the discovery of drugs with potential application for preventing and/or treating contemporary diseases. Thus, maintenance of induction above basal level of phase I and II detoxifying enzymes and antioxidants in host by plant extracts that may influence the carcinogenic process might provide means for interfering in the process and possibly diminish the overall occurrence of cancer in humans. According to one estimate about Rs. 900 crores worth herbal medicines are produced annually in India. According to Drug Controller-General of India, over 7000 licensed manufacturers supply 55,000 pharmacies and 14,000 herbal dispensaries with plant based products (Agrawal, 1998). Accordingly, screening traditional folklore plant resources that are indicative of potential human efficacy needs prioritization and their efficacy as orthodox medicament needs to be scientifically validated. Bearing in mind the pandemic nature of cancer, a proposal to screen such natural terrestrial products that can induce phase I and II detoxifying enzymes for disease
prevention needs to be considered. Many of these have known pharmacologic and therapeutic properties relevant to human health and most of them contain potent bioactive compounds. Since cancer claims six million lives each year and represents on a worldwide basis the single largest cause of death in both men and women, its prevention remains a keystone in the hierarchy of disease control.

Based on above mentioned background information, the purpose of the present study is to validate potential use of some terrestrial medicinal plant extracts in chemopreventive strategy by evaluating their biochemical basis of action according to classification scheme proposed by Wattenberg. This may be enumerated as -

1. Evaluating phase I microsomal heme proteins and associated enzymes in liver of experimental animals, fed with extracts of terrestrial medicinal plants included in this study.
2. Assessing their inducing potential of phase II conjugating enzymes especially glutathione S-transferase and DT-diaphorase in the liver and extrahepatic organs (lung, kidney and forestomach).
3. Evaluating amelioration of the antioxidant status by the modulators in liver of mice using test enzymes- superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and estimating the non-protein acid soluble sulphhydryl (-SH) level.
4. Evaluating the lipid peroxidation status in liver microsomes of animals treated with and without the test modulators.
5. Evaluating lactate dehydrogenase and relative organ weight as indices of modulator toxicity.

The following plant materials have been selected based upon ethnomedicinal survey carried out in Madhya Pradesh, one of the states of India and found to be used extensively by the tribals for alleviating common acute or chronic diseases;

a) Tinospora cordifolia  
b) Andrographis paniculata  
c) Adhatoda vesica  
d) Aloe vera
e) *Aegle marmelos*

f) *Clerodendrum inerme*

g) *Lawsonia alba*

h) *Prosopis juliflora*

i) *Decalepis hamiltonii*