5. SUMMARY & CONCLUSION...
The knowledge about prevention and treatment of cancer has increased enormously, yet the number of new cases is growing. It has been estimated that if the present trend continues, by 2020 cancer could kill around ten million people every year and the number of new cases each year could rise from 10.1 million in 2000 to 15.7 million in 2020 (WHO/UICC, 2003). The rising cancer incidences and mortality on the one hand and the limited efficacy of cancer treatment available on the other hand has led to focus on the preventive strategies. Among the various preventive strategies against cancer chemoprevention has received greater attention.

Chemoprevention is relatively new discipline in oncology. Chemopreventive strategy involves the use of drugs, biologics or nutrients to inhibit, delay or reverse the carcinogenesis. A remarkable progress has been made in developing chemoprevention strategies and understanding the mechanism/s of action of chemopreventive agents. A great strength of chemoprevention is that a large number of compounds can prevent the occurrence of cancer and a variety of mechanisms exist for obtaining such protection.

On the basis of current knowledge, it is believed that dietary habits play an important role in the prevention of cancer. There has been considerable scientific evidence, epidemiological and experimental, accumulated in these years indicating that a large number of naturally occurring compounds from plants, fruits, vegetables and other dietary substances possess efficacy to act as chemopreventive agents (Wattenberg, 1992; Tanaka, 1994).

Many chemopreventive agents of current interest such as genistein, curcumin, indole-3-carbinol, inositols, isothiocyanates, organosulphur compounds, resveratrol, retinoids, sulforaphane, squalene and terpenes are found in the diet and it is likely that these and other phytochemicals have a positive bearing on health. But a thorough understanding of the process of carcinogenesis and its modulation by plants and phytochemicals is necessary. Such endeavors would provide sound foundation for the studies to find out the mechanisms through which naturally occurring compounds
mediate protection from cancer, before the most effective dietary strategies for cancer prevention can be recommended for the general population.

With this backdrop, in the present work herbs investigated are important component of various traditional medicinal systems worldwide (Indian, Chinese, Turkish etc). These herbs namely *Phyllanthus emblica*, *Terminalia chebula*, *Terminalia belerica*, *Momordica charantia*, *Brassica sp.*, *Cuminum cyminum* and Triphala were evaluated for their chemopreventive efficacy in murine forestomach tumor model system.

Further, the modulatory influence of *Phyllanthus emblica*, *Terminalia chebula* and *Terminalia belerica* was assessed on hepatic phase I, phase II and antioxidant enzymes. The oxidative stress in tumor bearing forestomach and distant normal organs (Liver, kidney, spleen and heart) was also analyzed. Also the modulation of hepatic drug detoxification system due to forestomach tumor burden was analyzed.

Chemomodulatory and chemopreventive aspects of these herbs can be summarized as follow:

- All the herbs used (*Phyllanthus emblica*, *Cuminum cyminum*, *Brassica sp*, *Momordica charantia*, *Terminalia belerica*, *Terminalia chebula* and Triphala) showed cancer chemopreventive property in B(a)P induced forestomach tumorigenesis in murine model system but with varying effectiveness.

- Both the doses of Triphala effectively reduced the B(a)P induced forestomach tumor incidences in both short term and long-term treatment groups.

- Higher doses (5%) of *Phyllanthus emblica* (amla) and *Cuminum cyminum* (cumin) seeds of short-term treatment were most effective in inhibiting forestomach tumor incidences in Swiss albino mice.

- Both doses (2.5% and 5%) of *Phyllanthus emblica* and *Brassica sp* (Mustard seeds), and lower dose of *Momordica charantia* (Karela) for short-term treatment most effectively reduced the forestomach tumor burden (tumor/mouse).
• Long-term treatment of *Terminalia belerica* (Bahera) and *Momordica charantia* resulted in greater inhibition of forestomach tumor incidences compared to the shorter treatment group. But these long term treated group did not show any additional inhibition of tumor burden.

• All the three modulators (*Phyllanthus emblica*, *Terminalia belerica* and *Terminalia chebula*) tested, showed modulatory influence on the hepatic drug detoxification system, but with varying potentials.

• *Phyllanthus emblica* comes under dual acting category of chemopreventive agents as it has significantly decreased the content of cytochrome P450 and cytochrome b5 (phase I system) and enhanced the specific activity of GST and DTD (phase II system).

• All the doses of *Phyllanthus emblica* (2.5%, 5% and 10%) were equally effective in enhancing the levels of GSH and specific activity of SOD. But the activity of CAT was significantly increased by lower dose (2.5%) only. So the lower dose of *Phyllanthus emblica* seems most effective in enhancing the antioxidant status.

• All the doses of *Phyllanthus emblica* were effective in decreasing the Gly I activity and lipid peroxidation. While LDH activity was decreased significantly only by the higher dose (5% and 10%).

• 100μl dose of *Phyllanthus emblica* fruit juice for 15 days significantly increased the level of vitamin C in the hepatic tissue.

• Both the doses of *Terminalia chebula* (2.5% and 5%) increased the levels of hepatic cytochrome P450 and while only the higher dose increased the activity of cytochrome P450R.

• *Terminalia chebula* increased the GST activity at both the doses and activity of DTD with lower dose.

• *Terminalia chebula* belongs to the category of bifunctional chemopreventive agents as it induces hepatic phase I and phase II enzyme system.
• *Terminalia chebula* also significantly increased the level of GSH and activity of SOD and CAT.

• Both the doses of *Terminalia chebula* significantly decreased the lipid peroxidation. But only the higher dose significantly decreased the LDH activity.

• Both the doses of *Terminalia belerica* (2.5% and 5%) increased the levels of hepatic cytochrome P450 and while only the higher dose increased the activity of cytochrome b5R.

• *Terminalia belerica* increased the GST activity at the higher dose (5%) only.

• Even though *Terminalia belerica* has positive impact on hepatic phase I and phase II enzymes, but it is less effective compare to the *Terminalia chebula*.

• Both the doses of *Terminalia belerica* effectively increased the antioxidant content/activity (GSH, SOD and CAT) and decreased the activity of LDH and lipid peroxidation level.

• Among the three herbs tested, *Phyllanthus emblica* seems most effective in modulating the hepatic drug detoxification system, followed by *Terminalia chebula* and *Terminalia belerica*.

• The effective modulatory influence on hepatic drug detoxification system can be proposed as the reason for the comparative higher reduction of tumor burden by *Phyllanthus emblica*.

• Oxidative stress was observed in the tumor-bearing organ (forestomach). This is evident from the decreased in the activity of CAT, DTD and GST; and higher activity of LDH.

• Tumors in the forestomach also affected the antioxidant status of distant normal organs. The specific activity of GST was decreased in normal spleen, kidney, heart and liver of tumor bearing animals. But the level of GSH was increased in all the distant organs except liver, where GSH level decreased significantly.
• Forestomach tumor also affected the hepatic drug detoxification system. Cytochrome P450, cytochrome b5 levels; and activity of cytochrome P450R and GST were inhibited significantly. Thus forestomach tumor inhibited the drug detoxification system in the distant organ. This may be a crucial factor for the success of cancer chemotherapy.

These studies direct us for future advent in this area, which are listed below:

• Cancer chemopreventive efficacy of these herbs or their active principles in other epithelial carcinogenesis animal models such as mammary, colon, liver, prostate should be investigated.

• Strategies should be developed to prove that these agents are effective in other animal model systems also, so that they could be effectively used in clinical trials.

• To understand various mechanisms of actions of these chemopreventive agents especially at the molecular levels.

• Effective methods should be developed for the designing and use of new cancer chemopreventive agents.

• A firm basis should be established for the characterization and use of cancer chemopreventive agents in combination.