Despite recent advances in our understanding of the biological processes leading to the development of cancer, there is still a need for new and effective agents to bring cancer under control. The plants have been selected as an excellent source for new phytochemicals. Plants and plants based medicines have been used since the dawn of the civilization to maintain health and to treat a variety of diseases. Even though we enter the new century with its exciting prospect of gene therapy, herbal medicines remains one of the common forms of therapy available to much of the world population. Some of the chemotherapeutic agents which are currently in clinical use such as camptothecin, taxol, etoposide and vinca alkaloids are derived from plants. Epidemiological and animal studies revealed that several phytochemicals which are present in the fruits and vegetables of the normal dietary pattern has been appear to be protective against cancer. These agents suppressed the various events during the process of tumorogenesis like inflammation, activation of oncogenes, induce apoptosis of mutated cells, inhibit the aberrant signal transduction cascades, progression of mutated cell into a malignant clone etc. Because of their pharmacological safety plants and its derived compounds can be used either alone or as adjuncts to current chemotherapeutic agents to enhance their therapeutic effects. They can also used to minimize the radiotherapy and chemotherapy induced toxicities. Plants have been also reported to inhibit the process of metastasis and invasion. Several plants and phytochemicals have been found to inhibit the process of angiogenesis and suppressed the expression of angiogenic target genes such as COX-2, VEGF and MMPs. Plants are shown to inhibit several protein kinases, inducible nitric oxides synthase and the expression of proinflammatory cytokines. Several molecules which are isolated from plants are identified as cancer chemopreventive agents. In the present study we evaluated the possible biological effects of \textit{Phyllanthus amarus}, Berberine, Curcumin and Picroliv against cancer. The plant \textit{P.amarus} is used in indigenous system of medicine such as Ayurveda and Unani to mainly combat the liver disorders. Curcumin is the major active ingredient of the plant \textit{Curcuma longa} and has
been shown to possess several pharmacological activities. Berberine was isolated from the plant *Berberis asiatica* and Picroliv was from *Picrorhiza kurroa*.

In the initial part of the study we had evaluated the antiviral activity of *P. amarus*, Berberine, Curcumin and Picroliv against Newcastle Disease Virus (NDV) and Egg Drop Syndrome 1976 (EDS76) virus in embryonated eggs. Both the viruses affect the poultry population and causes significant economic burden. The present study showed that all the four compounds were significantly reduced the replication of virus in the allantoic cavity. Moreover the compounds were found to decrease the viral titre and inhibited the virus induced cytopathic changes in the embryo. The antiviral activity against Poliovirus I was determined in Vero cells. The non-toxic concentrations of these four compounds were used. All the drugs showed significant antiviral activity against Poliovirus I. Out of the four drugs Curcumin was found to be most effective and at very low concentration of 2µg/mL it produced a viral inhibition rate of 73.46%.

To further investigate the possible use of these drugs in cancer prevention we used a viral carcinogenic model induced by Friend murine leukemia virus (FMuLv) in BALB/c mice and the effect of these four compounds in the initiation and progression of erythroleukemia were evaluated. This model is one of the best animal models available to study the stepwise leukemia progression due to the reproducibility of the sequential genetic mutations leading to transformation of infected erythroblasts. Newborn BALB/c mice were injected with Friend virus and on 14th day after viral inoculation, the administrations of the drugs were started. Administration of *P. amarus, Berberine, Curcumin* and Picroliv significantly enhanced the life span of erythroleukemia harboring animals. Anemia was prevailing in all the FMuLv injected animals and there was a reduction of anemic conditions after the treatment with *P. amarus, Berberine, Curcumin* and Picroliv. The body weight was also increased in treated animals. Analysis of gene expression showed that all these compounds inhibited the expression of Bcl-2 and induced the expression of p53.
expression of p53 varied between the treated groups. This could be one of the major mechanisms of their action in the inhibition of virally induced cancers. Moreover these compounds were found to suppress the over activation of Raf-Erk1 cascade indicating that they can act at the cellular level. *P.amarus* induced the expression of P45$^{NFE2}$, a negative regulator of erythroid proliferation, which is often found to lose during FMuLv induced leukemia indicating that *P.amarus* probably acts in the initiation stage of leukemia.

Cancer cells often possess an inherent tendency to evade apoptosis due to defects in multiple signal transduction pathways. This often results in failure of cancer therapy and drug resistance. We evaluated the apoptotic inducing property of *P.amarus* in vitro. *P.amarus* was found to be a potent inducer of apoptosis in DLA cells. The cells treated with *P.amarus* showed typical apoptotic morphology. The DNA isolated from the *P.amarus* treated cells showed a ladder like pattern when resolved in agarose gel. Gene expression analysis demonstrated that *P.amarus* inhibited the expression of Bcl-2 in DLA cells and induces the expression of caspases 3 which is proapoptotic in nature. Induction of caspase-3 and inhibition of Bcl-2 could be the major mode of action of *P.amarus*. *P.amarus* also induces apoptosis in HepG2 cells as seen from the change in the mitochondrial membrane potential and annexin staining. The annexin-propidium iodide staining revealed that *P.amarus* at a concentration of 500µg/mL was able to induce the apoptosis as most of the cell populations were in the early stages of apoptosis.

Both radiotherapy as well as chemotherapy possesses several side effects of its own and the damage to normal cells along with the tumor cells is the major toxicity associated with both the types of therapies. Protection of normal tissues is as important as the destruction of cancer cells in both radiotherapy and chemotherapy. An adjuvant could be able reduce the toxicity of both these therapies to the normal cells without interfering its tumor reducing potential. In the present investigations *P.amarus* was found to reduce the leucopenia induced by whole body irradiation. It enhanced the
bone marrow cellularity and the number of alpha-esterase positive cells which is a marker of maturing monocytes. In the blood, liver and intestine *P. amarus* enhanced the activity of various enzymes in the antioxidant defense system there by protected the mice from radiation induced oxidative damage. *P. amarus* also protected the membrane from peroxidative damage as seen from the reduced formation of lipid peroxides in serum and in the tissues. The administration of *P. amarus* also afforded protection to mouse chromosome as revealed from the reduced number of micronuclei formation and decreased percentage of chromosomal aberrations in the mouse bone marrow. The percentage of aberrations in radiation alone treated group was 50.25 ± 4.50 while that of the normal unirradiated group and *P. amarus* 750mg/Kg b. wt treated groups were 3.75 ± 0.95 and 28.25 ± 1.70 respectively indicating that administration of *P. amarus* could reduce the percentage of radiation induced chromosomal aberrations in the bone marrow. Histopathological analysis of intestinal sections taken from the radiation treated group showed damage in the intestinal wall, the morphology of villi is damaged and the columnar lining of intestinal wall got distorted. Edema was present along with infiltration of lymphocytes. Administration of *P. amarus* reversed most of these changes and protected the intestinal system from radiation induced changes.

Cyclophosphamide (CTX), belongs to the class of alkylating agents is commonly used as an antineoplastic drug for the treatment of breast cancer, lymphomas, childhood tumors, and many solid tumors. CTX is metabolized in the liver by microsomal enzymes (cytochrome P450) and some of the metabolic products were found to cause profound cytotoxicity along with tumor reduction. In the present evaluation we found that administration of *P. amarus* could decrease the myelosuppression induced by the treatment of CTX and enhanced the bone marrow cellularity and alpha-esterase positive cells. We also checked whether *P. amarus* interfere with the tumoricidal potential of CTX. It was found that *P. amarus* did not interfere with the antitumor potential of CTX in solid tumor model induced by DLA and in fact it synergistically activated the tumor reducing potential of CTX.
Most of the carcinogens needed activation in the body before it gets converted into its active form. A group of enzymes present in the microsomal enzymes namely Cytochrome P450 (CYP450) played an active role in the activation of carcinogens. The regulation of these enzymes may be one of the key mechanisms in cancer prevention and therefore potent inhibitors of these enzymes are good candidates as chemopreventive substances against cancer. *P. amarus* has been reported to possess significant anticarcinogenic activity against several tumors induced by chemicals. So it is worthwhile to evaluate the possible effects of *P. amarus* on drug metabolizing enzymes. We found that CYP450 enzymes induced by phenobarbitone such as CYP1A2, CYP2B1/2 and CYP1A1 were inhibited by *P. amarus* both in vitro as well as in vivo conditions. The treatment with CTX was found to elevate the activity of phase I enzymes and suppressed the activity of phase II enzymes. *P. amarus* inhibited the activity of phase I enzymes such as aniline hydroxylase and aminopyrene demethylase in vitro and enhanced the activity of phase II enzymes like GST. These observations supported that *P. amarus* was effective in suppressing the activity of cytochrome P450 enzymes which play a major role in carcinogen activation. So it could be possible that one of the mechanisms behind the anticarcinogenic potential of *P. amarus* is the inhibition of drug metabolizing enzymes. The exact mechanism of inhibition of Cytochrome P450 enzymes by *P. amarus* is not known at present. The inhibition of activity in vitro could be due to the direct inactivation of the enzyme and in vivo inhibition could be either due to direct inhibition of the enzyme activity or the inhibition of expression of enzyme activity induced by phenobarbitone and CTX.

*P. amarus* consists of several active ingredients. Presence lignans like phyllanthin and hypophyllanthin, polyphenols, flavonoids such as quercetin, astragalin and some ellgitannins like catechin and epigallocatechin were isolated from *P. amarus*. Many plant phenolic compounds showed excellent antioxidant activities also they are good inhibitors of lipid peroxidation. A variety of hydrolyzable tannins purified from *P. amarus* were found to be potent inhibitors of protein kinases thereby inhibit the signal transduction
pathways. These studies clearly showed that *P.amarus* could be used as a radio protector, chemo protector and an inhibitor of viral oncogenesis hence it is worthwhile to carry out a detailed clinical study to fully exploit the potential of *P.amarus* in cancer prevention and treatment.

Berberine, Curcumin and Picroliv are already known for their chemopreventive potential against several types of chemically induced cancers. The present study supports the possible cancer preventive role of these compounds especially in virally induced cancers and a more detailed investigation into the clinical use of these compounds is highly warranted.