LITERATURE REVIEW

1. Jamal et al., reviewed that Cancer Statistics in 2007, In Each year, the American Cancer Society (ACS) estimates the number of new cancer cases and deaths expected in the United States in the current year and compiles the most recent data on cancer incidence, mortality, and survival based on incidence data from the National Cancer Institute, Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics. A total of 1,444,920 new cancer cases and 5, 59, 650 deaths for cancers are projected to occur in the United States in 2007.

2. Eba Adou et al, (2010) reviewed that plant natural products have historically been very important to drug discovery and development, particularly in the anticancer field. This is illustrated by a discussion of the structures and activities of camptothecin and its analogues, paclitaxel (Taxol), the vinca alkaloids vinblastine and vincristine, and podophyllotoxin and its analogues. A description of the isolation of one new and three known cardenolides from the Madagascar plant Pentopetia androsaemifolia is then provided as an example of this approach to drug discovery. The paper concludes with a brief discussion of betulinic acid, an old compound which is being developed into an anticancer and anti-HIV agent, and ipomoeasss F, an interesting antiproliferative compound isolated from a plant collected in Suriname.

3. Arun, B; Frenkel, E P. et al (2001) studied that topoisomerase-I (topo-I) inhibitors are a new class of anticancer agents with a mechanism of action aimed at interrupting DNA replication in cancer cells, the result of which is cell death. Most, if not all, topo-I inhibitors are derivatives of the plant extract camptothecin. Topotecan is a derivative of camptothecin which has been structurally modified to increase water solubility. The pharmacokinetic profile of topotecan is usually characterised by a two-compartment model and is linear in the dose range of 0.5 - 3.5 mg/m². Current clinical trials suggest antitumour activity against a variety of human tumour types, including ovarian cancer, non-small cell lung cancer (NSCLC) and non-lymphocytic haematologic
malignancies. The main dose-limiting toxicity (DLT) is non-cumulative myelosuppression. Non-haematologic toxicities are usually mild. Based on several Phase I studies, the recommended Phase II dose was 1.5 mg/m²/day iv. for 5 days. Current Phase I and Phase II trials are evaluating the combination of topotecan with other chemotherapeutic agents to increase the therapeutic benefits of topotecan. The DLT in these trials is mainly myelosuppression.

4. Kantarjian, H et al. (1999) studied that topotecan is a semisynthetic, water-soluble derivative of camptothecin, which is a cytotoxic alkaloid extracted from plants such as Camptotheca acuminata. Topotecan has the same mechanism of action as irinotecan. It inhibits the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of the DNA strand, resulting in double strand DNA breakage and cell death. Unlike irinotecan, topotecan is found predominantly in the inactive carboxylate form at neutral pH and it is not a prodrug. As a result, topotecan has different antitumour activities.

5. Wan M.C. et al., (1971) reviewed that among many antimitotic natural anticancer agents, which induce G2/M phase cell cycle arrest of tumor cells, Paclitaxel (Taxolâ ) is the first compound to cause cell cycle arrest by promoting the assembly of microtubules in vitro both chemists and biologists have been drawn to this diterpene derivative due to its promising spectrum of antineoplastic activity, its unique mechanism of action and the synthetic challenge arose from complex and densely functionalized ring system features.

6. Fan, W. et al., (1999) studied that the docetaxel, a novel member of the taxoid family, has shown greater potency than paclitaxel in the treatment of advanced breast cancer and certain other solid tumors. The promising clinical activity of docetaxel has also promoted considerable interest in combining this drug with other antitumor agents. In this study, we assessed the cytotoxic interaction between docetaxel and doxorubicin administered at various schedules to human
breast and ovarian cancer cells. Through a series of in vitro assays including DNA fragmentation analyses.

7. Premalatha Balachandran et al., (2005) reviewed that an integrated approach is needed to manage cancer using the growing body of knowledge gained through scientific developments. Thousands of herbal and traditional compounds are being screened worldwide to validate their use as anti-cancerous drugs. The science of Ayurveda is supposed to add a step on to the curative aspects of cancers that have resemblance with clinical entities of arbuda and granthi mentioned in Sushruta samhita. Hence, an attempt is made in this review to discuss about the pathology and therapeutic management of various cancers described in Ayurveda. Review of literature on anticancer drugs of plant origin revealed identification of newer ayurvedic drugs that are not mentioned in the ancient texts. These new findings add up to ayurvedic science that has been developed through ages. In addition, details of experimental and clinical studies conducted on single and compound ayurvedic preparations for their anticancer efficacy strongly emphasize ayurvedic therapy as a scientifically driven one and not simply unconventional.

8. Patrick O Erah, et al., (2002) reviewed that the African Traditional Herbal Research Clinic located in Ntinda, Uganda is a modern clinic facility established to create a model space whereby indigenous herbal practitioners and healers can upgrade and update their skills through training and certification and respond to common diseases using African healing methods and traditions in a modern clinical environment. Traditional healers are the major health labor resource in Africa as a whole. In Uganda, indigenous traditional healers are the only source of health services for the majority of the population. An estimated 80% of the population receives its health education and health care from practitioners of traditional medicine.

9. Lanher M.C., et al., (1991) emphasized that Euphorbia is a genus of plants belonging to the family Euphorbiaceae. Euphorbia nerifolia is a very popular herb amongst practitioners of traditional herb medicine, widely used as a
decoction or infusion to treat various ailments including intestinal parasites, diarrhoea, peptic ulcers, heartburn, vomiting, amoebic dysentery, asthma, bronchitis, hay fever, laryngeal spasms, emphysema, coughs, colds, kidney stones, menstrual problems, sterility and venereal diseases. Moreover, the plant is also used to treat affections of the skin. In this chapter we explore those investigations related to their pharmacological activities.

10. Yerra rajeshwar et al., (2005) Evaluated the antitumor effect and antioxidant role of Mucuna pruriens (Family: Fabaceae) against EAC bearing Swiss albino mice. The effect of methanol extract of Mucuna pruriens (MEMP) on tumor growth and host’s survival time was studied by the following parameters: tumor volume, packed cell volume, viable and non-viable cell count and life span of the host. MEMP was administered at a 125 and 250mg/kg b.w. once a day for 14 days, after 24 h of tumor inoculation. Decrease in tumor volume, packed cell volume, and viable cell count were observed in MEMP treated animals when compared to EAC treated animals. Treatment with MEMP at a dose of 125 and 250mg/kg increased the mean survival time to 29.5 ± 0.55 and 34 ± 0.2 days respectively. The extract also decreased the body weight of the EAC tumor bearing mice. Hematological studies reveal that the Hb content was decreased in EAC treated mouse, whereas restoration to near normal levels was observed in extract treated animals. There was a significant decrease in RBC count and increase in WBC counts in extract treated animals when compared to EAC treated animals. The study was also extended to estimate the liver biochemical parameters such as LPO, GSH, and antioxidant enzymes like SOD, CAT etc. Treatment with MEMP decreased the levels of lipid peroxidation and increased the levels of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT). The results suggest that the methanol extract of Mucuna pruriens seeds exhibits significant antitumor and antioxidant effects in EAC bearing mice.

11. Ohkawa H, et al., (1989) studied the anticancer potential of seed extract of Ziziphus mauritiana in vitro by different cell lines (HL-60, Molt-4, HeLa and normal cell line HGF) by MTT assay as well as in vivo against Ehrich ascites carcinoma bearing Swiss albino mice was investigated. The extract was found to markedly inhibit the proliferation of HL-60 cells. Annexin and PI binding of
treated HL-60 cells indicated apoptosis induction by extract in a dose dependent manner. The cell cycle analysis revealed a prominent increase in sub Go population at concentration of 20 6g/ml and above. Agarose gel electrophoresis confirmed DNA fragmentation in HL-60 cells after 3 h incubation with extract. The extract also exhibited potent anticancer potential in vivo.

12. Kakkar P, et al., (1984) studied the effects of ROS generation have been postulated to be major contributors to lead-exposure related disease. The aim of the study was to investigate the effect of aqueous extract of wormwood (Artemisia absinthium) on oxidative stress in rats protractedly exposed to lead. Aqueous extract of wormwood plant was administered orally (200 mg.kg-1 body weight). Plasma vitamin C, E and non-protein thiol concentrations, red blood cells (RBC) thiobarbituric acid reactive substances, reduced glutathione levels and haemolysis test were evaluated. In addition, RBC antioxidant enzymes activities such as superoxide dismutases, catalase, glutathione peroxidase, glutathione reductase were also estimated.

13. Lowry H., et al., (1951) reviewed that activity and the simplicity of procedure possible with its use, it has not found great favor for general biochemical purposes. In the belief that this reagent, nevertheless, has considerable merit for certain application, but that its peculiarities and limitations need to be understood for its fullest exploitation, it has been studied with regard to effects of variations in pH, time of reaction, and concentration of reactants, permissible levels of reagents commonly used in handling proteins, and interfering substances. Procedures are described for measuring protein in solution or after precipitation with acids or other agents, and for the determination of as little of protein.

14. Patel Rajesh M, et al, (2011) studied that many coumarins and their derivatives exert anti-coagulant, anti-tumor, anti-viral, anti-inflammatory and antioxidant effects, as well as anti-microbial and enzyme inhibition properties. The different substituents in the coumarin nucleus strongly influence the biological activity of the resulting derivatives. Although some coumarins have been already characterized to evoke a particular biological activity, the challenge would be the design and
synthesis of new derivatives with high specific activity against different forms of free radicals and define their mechanism of action to achieve new therapeutic drugs against disorders results from oxidative damage. The present research work were evaluated for in vitro antioxidant activity by DPPH, super oxide and nitric oxide free radical scavenging assay methods. From results of DPPH, super oxide and nitric oxide methods, it found that compound I and II displayed strong antioxidant (P < 0.001) activity compared to the ascorbic acid.

15. Gutteridge C, et al (1995) reviewed that free radicals of different forms are constantly generated for specific metabolic requirement and quenched by an efficient antioxidant network in the body. When the generation of these species exceeds the levels of antioxidant mechanism, it leads to oxidative damage of tissues and biomolecules, eventually leading to disease conditions, especially degenerative diseases.

16. Mohammad I., et al (2009) reviewed that many natural as well as synthetic coumarins and more complex related derivatives have recently drawn much attention due to its broad pharmacological activities include anti-bacterial, anti-thrombotic and vasodilatory, antimutagenic, lipoxygenase and cyclooxygenase inhibition, scavenging of reactive oxygen species, and anti-tumourigenic, appears to be based on the coumarin nucleus.

17. Von Hoff, D. D. et al, (1997) studied that the cytotoxic effect of docetaxel is primarily due to its ability to promote tubulin assembly and inhibit microtubule depolymerization. Similar to paclitaxel, the first member of the taxoid family used in clinical studies, docetaxel also acts as a mitotic spindle poison and induces a mitotic block in proliferative cells.

18. Hennnequin, C., et al (1998) studied that in vitro studies have shown that docetaxel has a broad spectrum of activity against a variety of tumor types, including breast cancer, ovarian cancer, non-small cell lung cancer, head and neck cancer, colorectal cancer, and melanoma.
19. Lavelle, F., et al (1995) studied that *in vivo* experiments in animal models and clinical trials have also shown that docetaxel is more potent than paclitaxel in the treatment of advanced breast cancer and other solid tumors.

20. Khayat, D., et al (1999) reviewed that Combination therapy with multiple drugs is a common practice in the treatment of cancer. The promising clinical activity of docetaxel has promoted considerable interest in combining this drug with other antitumor agents, such as etoposide, cyclophosphamide, 5-fluorouracil, and doxorubicin. A number of these docetaxel-containing combinations are currently undergoing clinical evaluations, and preliminary results appear to be encouraging.

21. Henderson, I. C. et al (1991) explain that Doxorubicin, a derivative of anthracyclines, is one of the most active agents with a broad spectrum of activity against solid tumors and hematological malignancies. The combination of docetaxel and doxorubicin has been proven effective in first-line treatment of metastatic breast cancer, with high response rates and acceptable toxicity.

22. Su Zeng, et al (2000) studied that *in vitro* evaluations of the cytotoxic effects of docetaxel and doxorubicin against human breast and ovarian tumor cells *in vitro*. Our results demonstrated that pretreatment of tumor cell with doxorubicin or simultaneous exposure of tumor cell to doxorubicin could significantly repress the cell-killing activity as well as the general cytotoxic effect of docetaxel against tumor cells *in vitro*. These findings indicate that the interaction between docetaxel and doxorubicin is highly schedule dependent. The optimal schedule of this combination might be sequential exposure to docetaxel followed by doxorubicin.

23. Premalatha Balachandran et al (2005) reviewed that an integrated approach is needed to manage cancer using the growing body of knowledge gained through scientific developments. Thousands of herbal and traditional compounds are being screened worldwide to validate their use as anti-cancerous drugs. The science of Ayurveda is supposed to add a step on to the curative aspects of cancers that have resemblance with clinical entities of *arbuda* and *granthi* mentioned in *Sushruta*. 
Hence, an attempt is made in this review to discuss about the pathology and therapeutic management of various cancers described in Ayurveda. Review of literature on anticancer drugs of plant origin revealed identification of newer ayurvedic drugs that are not mentioned in the ancient texts. These new findings add up to ayurvedic science that has been developed through ages. In addition, details of experimental and clinical studies conducted on single and compound ayurvedic preparations for their anticancer efficacy strongly emphasize ayurvedic therapy as a scientifically driven one and not simply unconventional.

24. Hartwell JL. et al (1969) reviewed that cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century. In the United States, as the leading cause of death, it accounts for 25% of all the deaths in humans presently. It is considered as an adversary of modernization and advanced pattern of socio-cultural life dominated by Western medicine. Multidisciplinary scientific investigations are making best efforts to combat this disease, but the sure-shot, perfect cure is yet to be brought into world medicine. Recently, a greater emphasis has been given towards the researches on complementary and alternative medicine that deals with cancer management. Several studies have been conducted on herbs under a multitude of ethno botanical grounds.

25. Pandey G. et al (2002) reviewed that Hartwell has collected data on about 3000 plants, those of which possess anticancer properties and subsequently been used as potent anticancer drugs. Ayurveda, a traditional Indian medicine of plant drugs has been successful from very early times in using these natural drugs and preventing or suppressing various tumours using various lines of treatment.

26. Bhishagratha KL. et al (1991) emphasized that Charaka and Sushruta samhitas, two well-known Ayurvedic classics, describe cancer as inflammatory or non-inflammatory swelling and mention them as either Granthi (minor neoplasm) or Arbuda (majorneoplasm). Ayurvedic literature defines three body-control systems, viz., the nervous system (Vata or air), the venous system (Pitta or fire), and the arterial system (Kapha or water) which mutually coordinate to perform the normal function of the body. In benign neoplasm (Vataja, Pittaja or Kaphaja ) one or two
of the three bodily systems are out of control and is not too harmful because the body is still trying to coordinate among these systems. Malignant tumours (Tridosaja) are very harmful because all the three major bodily systems lose mutual coordination and thus cannot prevent tissue damage, resulting in a deadly morbid condition

27. Sankaran PS. et al (1976) reviewed that according to Sushruta, the fundamental cause of major neoplasm is the pathogens that affect all parts of the body. He called the sixth layer of the skin as ‘Rohini,’ (epithelium) and pathogenic injuries to this layer in muscular tissues and blood vessels caused by lifestyle errors, unhealthy foods, poor hygiene and bad habits results in the derangement of doshas, which leads to the manifestation of tumours.

28. Sastry JLN, et al (2001) reviewed that pathogenesis in Ayurveda is explained on the basis of Tridoshas. Agni or Pitta, which is present in each and every cell, is responsible for digestion and metabolism in human body. The decrease in agni is inversely proportional to the related tissue and therefore in arbuda, the decreased state of dhatwagni (deranged metabolism) will result in excessive tissue growth. Vata can be correlated with the anabolic phase of growth whereas kapha to the catabolic phase. Cancer originates due to a metabolic crisis, i.e. aggravation of vata forces and suppression of kapha forces, both interacting with one another resulting in proliferation. However, the abnormal cancerous growth at a specific organ (Ekadesavridhi) is managed by compensation from other parts of the body (Anyasthaniyakshaya), e.g. body weight loss (cachexia).

29. Thatte U, et al (2001) reviewed that abuse of nature’s law upsets the human system and ends up in disease like cancer. It is again the nature, the foremost physician who brings the cure. The Ayurvedic system of medicine was well founded on the basic principles of nature and its elements after a careful and thorough study of human physiology. This is the first system to emphasize health as the perfect state of physical, psychological, social and spiritual component of a human being. The therapeutic approach of Ayurveda has been divided into four categories as Prakritisthapani chikitsa (health maintenance), Roganashani chikitsa (disease
cure), Rasayana chikitsa (restoration of normal function) and Naishthiki chikitsa (spiritual approach).

30. Sankaran PS, et al (1976) emphasized that when medical treatment practices fail, then the case was left to surgeons. Surgical cancer management in Ayurveda include the principles of fomentation by means of external application, cleansing by internal medication, treatment to liquefy the contents of the swelling, opening the tumour surgically for evacuation of its contents, cauterisation to avoid recurrence and post-operative care for healing the wound.

31. Treadway S, et al (1998) emphasized that herbal decoctions consisting of multiple herbs each possessing tremendous potential for a cancer cure are commonly used in Ayurveda. These formulations are reported to work on multiple biochemical pathways and are capable of influencing several organ systems simultaneously. The benefit of an herbal decoction is that it can nourish the body as a whole by supporting various organ systems.

32. Trivedi N, et al (1998) studied that the extract and isolated diterpenes (andrographiside and neoandrographolide) from this plant are proved to be beneficial against tumourigenesis by their anti-lipoperoxidative action and by enhanced carcinogen detoxification action.

33. Shirin H, et al (2001) reviewed that water-soluble derivative of garlic, S-allylmercaptocysteine (SAMC), inhibited proliferation and cell cycle progression in two human colon cancer cell lines, SW-480 and HT-29, similar to the effects of sulindac sulfide (SS), a well-known colon cancer chemopreventive agent. Co-administration of SS with SAMC enhanced the growth inhibitory and apoptotic effects of SS, suggesting the usefulness of SAMC alone or in combination with SS or other chemopreventive agents.

induced skin reactions, the median time of five weeks was taken to show any skin changes in the aloe/soap treatment versus three weeks in the soap only treatment. The protective effect of adding aloe to the soap regimen increases during long time radiation exposure.

35. Vrinda B, et al (2001) concluded that Orientin and Vicenin, two water-soluble flavonoids isolated from the leaves of *Ocimum sanctum* have shown significant protection to the human lymphocytes against the clastogenic effect of radiation, radiation lethality and chromosomal aberrations in vivo. This radioprotection associated with their antioxidant activity may have clinical potential in cancer therapy.

36. Praveenkumar V, et al (1994) studied that *W. somnifera* when administered for 4 days before paclitaxel treatment and continued for 12 days caused significant reversal of neutropenia of paclitaxel in mice. It can be used as an adjuvant during cancer chemotherapy for the prevention of bone marrow depression associated with anticancer drugs. The active component, withaferin A isolated from the extract showed significant antitumour and radiosensitising effects in experimental tumours.

37. Bakhru HK, et al (2000) reviewed that ayurvedic anticancer therapy includes recommendations for use of specific foods and herbs which are very helpful not only in preventing the progression of the disease but also makes the patients feel better and comfortable overcoming the symptoms. *Allium sativum* (garlic) could be helpful to manage pain and ache. *Bacopa monniera* strengthens mental faculties and helps to manage insomnia or sleeplessness due to stress.

38. Office of Alternative Medicine (1994) reviewed that ayurvedic practitioners and researchers in medical sciences can help to improve this medicine by increasing their involvement and contribution. Case study is the research design, which can form basis for future research directions and can provide valuable contributions to the medical field with minimal cost budgets. Case studies have also been suggested by the NCCAM (National Center for Complementary and Alternative Medicine, Bethesda, USA) as a means to determine whether a complementary anticancer
therapy demonstrates potential efficacy against particular cancer and whether clinical development of the therapy should continue.

39. Deepa Philip et al (2011) performed each of the extracts & checked the % viability. The mean of the cell viability values was compared to the control to determine the effect of the extract on cells and % cell viability was plotted against concentration of the plant extract. The minimum concentration of plant extract that was non-toxic to 3T3 cells but toxic to HepG2 cells was recorded as the effective drug concentration.

40. Ali Yildirim et al (2001) studied the antioxidant activity & determined by the thiocyanate method. Each sample (containing 200-1000µg extract) in 0.5 mL of distilled water was mixed with 2.5 mL of linoleic acid (Sigma) emulsion (0.02M, in 0.04M pH 7.0 phosphate buffer) and 2 mL phosphate buffer (0.04M, pH 7.0) in a test tube and incubated in darkness at 37°C. The amount of peroxide was determined by reading absorbance at 500 nm after colouring with FeCl2 and thiocyanate at intervals during incubation a-Tocopherol (Sigma) was used as standard antioxidant.