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A Review on Anticancer Natural Drugs

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Abstract: Cancer is a major public health burden in both developed and developing countries. It is an abnormal growth of cells in body that can lead to death and globally the numbers of cancer patients are increasing day by day. There are several medicines available in the market to treat the various types of cancer but no drug is found to be fully effective and safe. Many natural products and their analogues have been identified as potent anti-cancer agents and day by day the anti-cancer property of various plants is being identified. New drug discovery is time consuming & laborious process. So the anticancer activity of certain natural products and their analogs can be enhanced by synthesizing new derivatives based on active pharmacophore models; drug resistance & solubility & metabolic limitations can be overcome by appropriate molecular modification. Medicinal plants with their isolated lead molecules are also used as an alternative medicine for treating neoplastic cells. Neoplastic cells are the anomalous proliferation of cells in the body which cause cancer. Diverse efficient compounds derived from natural products have been isolated as anticancer agents. There chemical compounds are formulated with a view to create effective drugs against cancer.
Keywords: Cancer, Chemotherapy, cancer cells, natural products, plants, Medicinal plants, Herbal medicine.

Introduction:-

Natural products especially plants have been used for the treatment of various diseases for thousands of years. Terrestrial plants have been used as medicines in Egypt, China, India and Greece from ancient times and an impressive number of modern drugs have been developed from them. The first written records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Acadians[1]. Among the human diseases cancer is one, probably the most important genetic disease which can be treated with medicinal plants. Every year, millions of people are diagnosed with cancer, leading to death in a majority of the cases. Cancer is the abnormal growth of cells in our bodies that can lead to death. Cancer cells usually invade and destroy normal cells. These cells are born due to imbalance in the body and by correcting this imbalance, the cancer may be treated. Billions of dollars have been spent on cancer research and yet we do not understand exactly what cancer is[2]. Every year, millions of people are diagnosed with cancer, leading to death. According to the American Cancer Society deaths arising from cancer constitute 2–3% of the annual deaths recorded worldwide. Thus cancer kills about 3500 million people annually all over the world. Several chemo preventive agents are used to treat cancer, but they cause toxicity that prevents their usage[3]. The increasing costs of conventional treatments (chemotherapy and radiation) and the lack of effective drugs to cure solid tumors encouraged people in different countries to depend more on folk medicine which is rooted in medicinal plants use. Such plants have an almost unlimited capacity to produce substances that attract researchers in the quest for new and novel chemotherapeutics. Of over 2069 anti-cancer clinical trials recorded by the National Cancer Institute as being in progress as of July 2004, over 160 are drug combinations including these agents against a range of cancers[4].

Cancer and its Classification:-

Cancer is a general term applied of series of malignant diseases that may affect different parts of body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth or tumor, or proliferate throughout the body, initiating abnormal growth at other sites. If the process is not arrested, it may progress until it causes the death of the organism. The main forms of treatment for advance stage cancer in humans are surgery, radiation and drugs (cancer chemotherapeutic agents).Cancer chemotherapeutic agents can often provide temporary relief of symptoms, prolongation of life, and occasionally cures[5]. In recent years, a lot of effort has been applied to the synthesis of potential anticancer drugs. Many hundreds of chemical variants of known class of cancer chemotherapeutic agents have been synthesized but have a more side effects. A successful anticancer drug should kill or incapacitate cancer cells without causing excessive damage to normal cells. This ideal is difficult, or perhaps impossible, to attain and is why cancer patients frequently suffer unpleasant side effects when under-going treatment[6]. However, a waste amount of synthetic work has given relatively small improvements over the prototype drugs. There is a continued need for new prototype-new templates to use in the design of potential chemotherapeutic agents: natural products are providing such templates. Recent studies of tumor-inhibiting compound of plant origin have yielded an impressive array of novel structures[7].

Types of Cancers[8]:-

1) **Cancers of Blood and Lymphatic Systems**

a) Hodgkin's disease, b) Leukemia's, c)Lymphomas, d) Multiple myeloma, e) Waldenstrom's disease

2) Skin Cancers

a) Malignant Melanoma

3) Cancers of Digestive Systems

a) Esophageal cancer b) Stomach cancer c) Cancer of pancreas d) Liver cancer e) Colon and Rectal cancer f) Anal cancer

4) Cancers of Urinary system

a) Kidney cancer b) Bladder cancer c) Testis cancer d) Prostate cancer

5) Cancers in women

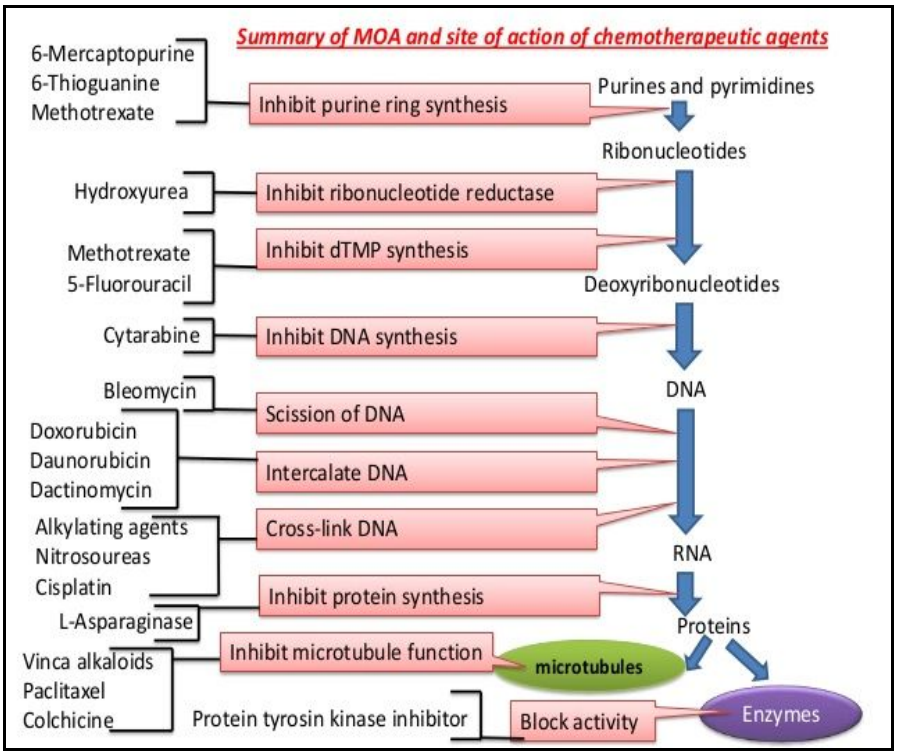
a) Breast cancer b) Ovarian cancer c) Gynecological cancer d) Choriocarcinoma

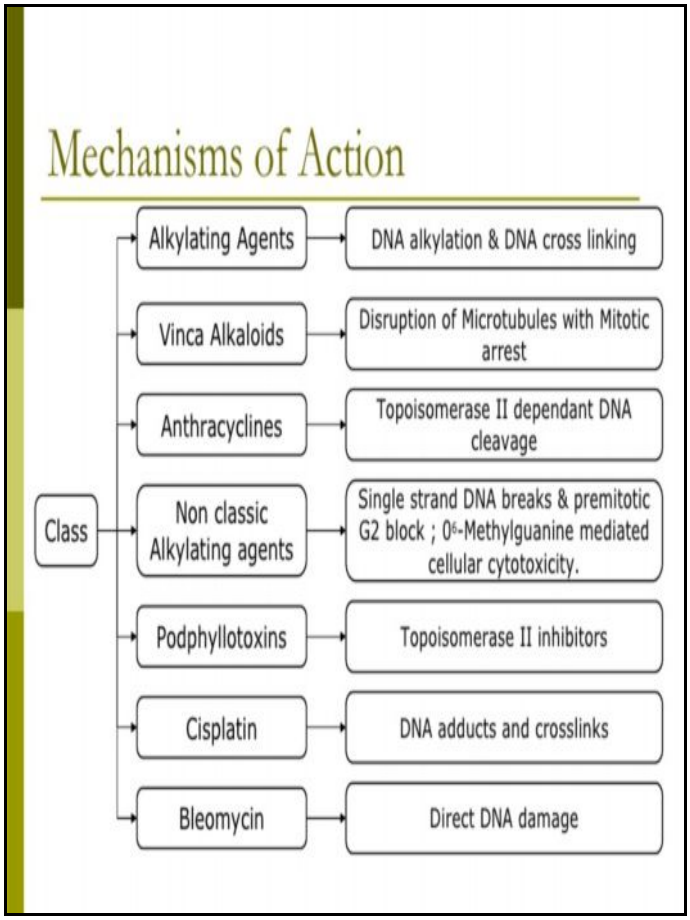
6) Miscellaneous cancers

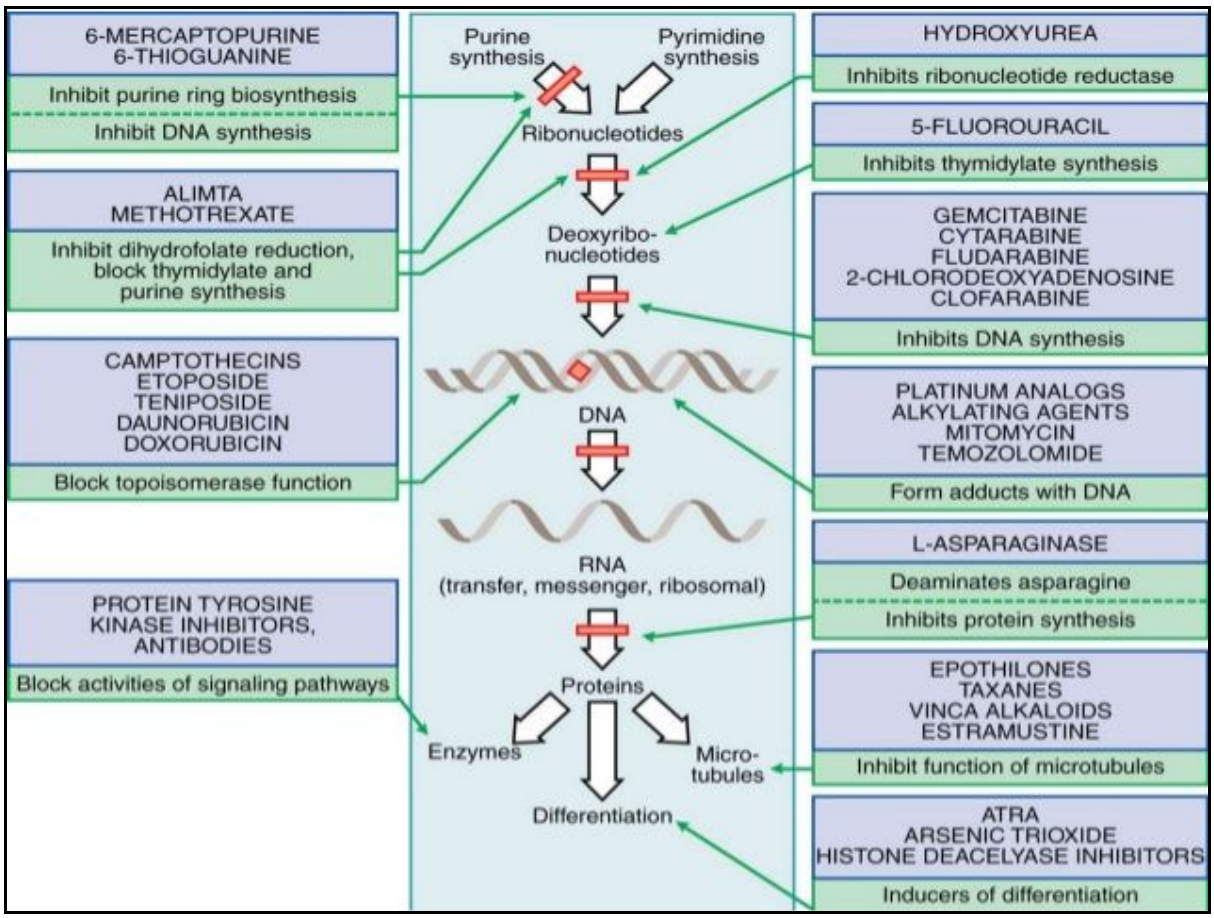
a) Brain cancer b) Bone cancer c) Characinoid cancer d) Nasopharyngeal cancer e) Retroperitoneal sarcomas f) Soft tissue cancer g) Thyroid cancer

Breast cancer is the most common form cancer in worldwide. Amongst south African women, breast cancer is likely to develop in one out of every 31 women in the country. Breast cancer in India is the second most common cancer in women after the cancer of uterine cervix[7].

The Mechanism on Cancer Therapy[9]:-







Chemotherapy:-

Although adjuvant CTX is frequently used for primary tumors, its main use is to control overt disseminated disease. The excessively active growth-signaling pathways in cancer cells makes them susceptible to a wide range of drugs which target growth-signaling molecules and/or processes involved in cellular replication and expression . However, as these processes also drive normal cells, the effect is preferential and not exclusive, which results in the unwanted side effects seen with these agents. Cells which are normally actively dividing, in particular the bone marrow constituents and those of the intestinal lining, are particularly susceptible. Disregulated cell cycle events, due to mutations in cancer cells, do sometimes offer opportunities to target those cells without affecting normal cells. The relatively wide spectrum of activity of cytotoxic drugs makes them a rather harsh and non-specific form of treatment that can only be tolerated for short periods. Indeed the effects of the treatment may sometimes cause more distress than the disease. These side-effects include dry flaky skin, loss of hair, nausea and vomiting, changes in taste and appetite, blood clotting problems, fatigue, depressed immune system and possible sterility[10].

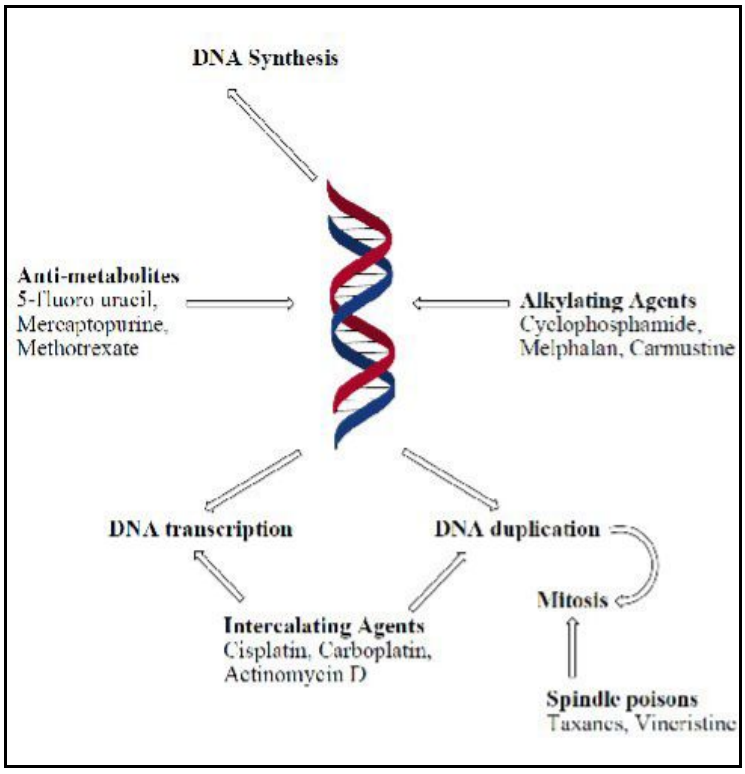


Fig no 1 : Sites of action of cytotoxic agents[10]

Oncogenes and tumor suppressor genes[4]:-

Two sets of genes are controlling cancer development. Oncogenes are the first set of genes and are involved in different cell activities including cell division. However, over expression of these genes transforms a normal cell into a cancer cell. On the other hand, the second set of genes (tumor suppressor genes) inhibits cancer cell formation by different mechanisms. Tumor suppressor genes are under expressed in cancer cells while, oncogenes are over expressed[11]. Table 1 summarizes the main oncogenes and tumor suppressor genes and their role in cancer development. Oncogenes and their products represent good targets for Cancer therapy. Other targets include enzymes involved in cell division like topoisomerases that unwind the DNA during replication. The diversity of plant derived natural products can provide therapeutic products attacking different targets in cancer cells[12].

Plant Derived Anti-Cancer drugs:-

1. Vinca Alkaloids: The first agents introduced in clinical use were vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the *Catharanthus roseus*. (Apocynaceae).These drugs were discovered during an investigation for oral hypoglycemic agents. While research investigators could not confirm this activity, it was noted that plant extracts reduced significantly white blood cell counts and also caused bone marrow depression in rats[13]. Plant extract also prolong the life of mice bearing a transplantable lymphocytic leukemia. The plant was originally endemic to Madagascar, but the samples used in the discovery of vincristine and vinblastin were collected in Philippines and Jamaica. Recently semi-synthetic analogues of vinca alkaloids are vinorelbine (VRLB) and vindesine (VDS). These are primarily using alone or in combination with other chemotherapeutic drugs to combat a variety of cancers. VLB is using for the treatment of lymphomas, leukemias, breast cancer, testicular cancer, lung cancers, and Kaposi's sarcoma. VCR had also showed efficacy against leukemia, particularly acute lymphocytic leukemia in childhood[14].

2. Podophyllotoxin Derivatives : The species of Podophyllaceae family such as *Podophyllum peltatum* Linn., *Podophyllum emodii* have been reported with a long history of therapeutical use, including the treatment of skin cancers and warts. *Podophyllum peltatum* have been used by the Native Americans for the treatment of "cancer"[15]. The interest was promoted by the observation in the 1940s that an alcohol extract of the dried roots (called podophyllin) cures venereal warts by topical application. The chief cytotoxic therapeutic constituents

were identified as podophyllotoxins and have been first isolated in 1880, but its correct structure could only be elucidated in the 1950s with the advancement in spectroscopic techniques. Other closely related podophyllotoxins like lignans were also isolated during this period and became introduced into clinical trials, but they were dropped due to lack of efficacy and unacceptable toxicity. Extensive research studies at Sandoz Laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinical agents which are being used in the treatment of lymphomas and bronchial and testicular cancers. Of 2069 anti-cancer clinical trials recorded by the NCI as being in progress as of July 2004, over 150 are drug combinations including etoposide against a range of cancers[16].

3. Allium Sativum (Allicin): *Allium sativum* (garlic, lasun) is used to treat a wide variety of diseases in India. Allicin is a major component of raw garlic and ajoene is a product of the rearrangement of allicin. Its cytotoxic effect has been tested using human primary fibroblasts, a permanent, nontumorgenic cell line derived from baby hamster kidney cells and a tumorgenic lymphoid cell line derived from a Burkitt lymphoma. The cytotoxic action was in the range 2-50 μg/ml[17]. Some organo-sulfur compounds from garlic, like S-allylcysteine, are reported to retard the growth of chemically induced and transplantable tumors in several animal models[18]. Administration of garlic (250 mg/kg, p.o., thrice a week) in male wistar rats, has been significantely suppressed 4-nitro quinoline-1-oxide induced tongue carcinogenesis as revealed by the absence by the carcinomas in the initiation phase and their reduced incidence in the post initiation phase[19]. Thus the consumption of garlic may beneficial providing some kind of protection from cancer.

4. Andrographis Paniculata : Phytochemical investigation of the ethanol extract of the aerial parts of *Andographis paniculata* has been reported the isolation of 14 compounds; a majority of them are flavonoids and labdane diterpenoids. The cytotoxic activities of these compounds have been evaluated against various cell lines and found that these isolates have a potent tumour inhibitory activity against all investigated cell lines[20]. The methanol extract of *Andrographis paniculata* was fractionated, dichloromethane fraction reported to possess three active constituents which were further tested and exhibited cytotoxic activity and also potent immunostimulating activity[21]. However, there were also its adverse side effects were also reported which may include gastric upset, headache, bitter taste and fatigue. High doses of *Andographis paniculata* may have affect the normal functions of liver[22].

5. Annona Muricata : Graviola is known by its scientific name, *Annona muricata*. The important class of medicinal components found in graviola is acetogenins. Acetogenins was found in the fruit, seeds, leaves, and bark of the graviola plant. Preliminary research showed that acetogenins block production of adenosine triphosphate, which inhibits the pump that removes cancer drugs from the cell, allowing chemotherapy to be more effective. Furthermore, research suggested that acetogenin may have chemotherapeutic potential, especially against cancer that resistant to multiple drugs[23]. Parkinson like symptoms can occur on oral ingestion of graviola [24]. Some specific acetogenins have been reportedly identified to be toxic for various cancer cell lines like lung solid human-breast cancer, tumor carcinoma, pancreatic carcinoma, prostatic adenocarcinoma, colonic adenocarcinoma, human lymphoma, liver cancer, and multiple-drug resistant human-breast adenocarcinoma.

6. Apis Mellifera: *Apis mellifera* is the scientific name of honey bee, from which honey is produced. Honey is used to hasten healing of skin wounds, ulcerations, and burns in Indian system of medicine. A protein of the honeybee *Apis mellifera* has been reported to enhance proliferation of primary-cultured rat hepatocytes and also suppresses apoptosis[25]. It has also showed cytotoxicity in normal human lymphocytes and HL-60 cells. Hamzaoglu *et al.* (2000) implanated cancer cell into neck wounds of mice, then divided mice into two groups. A significant decrease in wound cancer tumors were observed in the groups of mice that were treated with surgical wounds coated with honey pre and postoperatively. This finding may have some application in human surgery .

7. Bidens Pilosa : *Bidens pilosa* is a folk medicine reported with the presence of polyacetylenes, flavonoids, terpenoids, phenylpropanoids and others. An extensive research work on different sextracts of *Bidens pilosa* and further fractionation led to the isolation and characterization of potential marker compound phenyl-1,3,5-heptatriyne. This marker compounds revealed the toxicity profile on normal blood cells in erythrocyte osmotic fragility experiments along with other extracts. Hexane, chloroform and methanol extracts of *Bidens pilosa* and their fractions were tested on various cancer cell lines. Results exhibited the antitumor activity of extracts among which hexane extract pronounced the most remarkable activity[26].

8. Bolbostemma Paniculatum : Extraction and further fractionation of chinese herb *Bolbostemma paniculatum* (Cucurbitaceae) led to the isolation and characterization of a triterpenoid saponin Tubeimoside-V. Further investigations on tubeimoside-V revealed the apoptotic killing nature on glioblastoma cells, thus suggesting its critical role in antitumor chemotherapy. Other tubeimosides like tubeimodes-I, tubeimoside-II and tubeimoside-II also exhibited promised cytotoxic activity which may be linked to the inhibition of DNA synthesis and may induce phenotypic reverse transformation of tumor cells[27].

9. Cannabis Sativa : *In vitro* studies of components of marijuana (*Cannabis sativa*) indicate a potential to inhibit human breast cancer cells and to produce tumor eradications. In experiments introducing marijuana to malignant brain tumors, it was found that survival of animals was increased significantly .The active components of *Cannabis sativa*are cannabinoids. Cannabinoids and their derivatives exert palliative effects in cancer patients by preventing nausea, vomiting and pain and also stimulated the appetite. These compounds have also been shown anti-tumor activity in cell culture and animal models by modulating key cell-signalling pathways[28].

10. Daphne Mezereum : *Daphne mezereum* is a plant widely used as afolklore remedy for treating cancer like symptoms. A hydro alcohol extract of *Daphne mezereum*has exhibited a potent antileukemic activity against lymphocytic leukemia in mice. Further fractionation studies on the extract resulted in the isolation and characterization of mezerein as a potent antileukemic compound [29].

11. Gossypium Hirsutum : *Gossypium hirustum* or *Gossypium herbaceum*also called as Gossypol or cottonseed oil and used as a male contraceptive, in the treatment of metastatic carcinoma of endometrium or ovary and also used in HIV. Some *in vivo* and *in vitro* studies revealed the antitumor properties of gossypol on many cytosolic and mitochondrial enzyme systems that is fundamental for tumor cell growth, including melanoma, endometrial, colon, lung, prostate, breast, brain, and adrenocortical cancer[31]. However no typical dose is yet suggested for the treatment of cancer and self-medication with gossypol is not safe because of its potential toxicity[32] .

12. Nervilia Fordii : *Nervelia fordii* is a drug used in China as a folklore remedy. Petroleum ether and ethyl acetate extracts of *Nervilia fordii* has been screened out for its anticancer properties using mice models. Both extracts have shown prominent anticancer effects when administered to S-180 mice and H-22 mice models; also prolong the life of cancer bearing mice. This study suggests, *Nervilia fordii* can exploit as cancer inhibiting agent and further research work is required to isolate active constituent/s present in drug[33] .

13. Salvia Miltiorrhiza : Tanshinone-I was isolated from traditional herb *Salvia miltiorrhiza*e, was investigated on the expression of intercellular adhesion molecule. The study revealed a potential anticancer effect of tanshinone-I on breast cancer cells, suggesting that tanshinone-I may serve as an effective drug for the treatment of breast cancer[34]. Tanshinone II-A, isolated from *Salvia miltiorrhiza,* induced apoptosis which was linked to proteolytic cleavage of a major component in apoptotic cell death mechanism[35] .

14. Terminalia Chebula : *Terminalia chebula*is a source of hydrolysable tannis and its antimutagenic activity in *Salmonella typhimurium*has been documented[36].Phenols like chebulinic acid, tannic acid, ellagic acid are the cancer growth inhibitors found in the fruits of *Terminalia chebula* [37]. *Terminalia chebula* fruits powder and its acetone extract of bark have been reported with promising antimutagenic and anticarcinogenic activity [38].

15. Zingiber Officinale : *Zingiber officinale* ethanol extract was investigated to find out its antitumor effects in skin tumorigenesis model. Pre-application of *Zingiber officinale* ethnol extract onto the skin of mice resulted in significant inhibition of 12-0-tetradecanoylphorbol- 13-acetate (TPA)-caused induction of epidermal ODC, cyclo oxygenase, and lipoxygenase activities and ODC mRNA expression in a dosedependent manner. Pre-application of *Zingiber officinale*ethanol extract to mouse skin also resulted in a significant inhibition of TPA caused epidermal edema and hyperplasia. In prolonged time studies, topical application of *Zingiber officinale* ethanol extract thirty minute prior to that of each TPA application to 7, 12-dimethylbenz(a)anthracene initiated mice caused amarked protection against skin tumor incidence its multiplicity[39].

Ginger's natural bio-actives, specifically ginger extract and 6-gigerol, have also been investigated for their *in vitro* inhibition of two key aspects of colon cancer biology, cancer cell proliferation and angiogenic potential of endothelial cell tubule formation. These active ginger constituents linked to a direct effect on

cancer cells. Among other compounds, 6-gingerol was found more effective even at lower doses resulted in inhibition of endothelial cell tube formation[40] .The suggested mechanism of action of Ginger extract on colon cancer cells may be its suppression and arresting the G0/G1-phase, reducing DNA synthesis and inducing apoptosis [41].

List of Anticancer plants[5]:

Sr.No:	Plant Name/Family	Habitat	Active constituent	Class
1.	*Agapanthus africanus* Agapanthace	S.Africa	Isoliquiritigenin	Chalcone
2.	*Aglaila sylvestre* Meliaceae	India	Silvesterol	----------
3.	*Ailanthus Altissima* Simaraubaceae	China	Ailnthone, Ailantenol	Quassinoids
4.	*Apium graveolens* Umbelliferae	N.America	Apigenin	Flavonoid
5.	*Bleckeria vitensis* Apocynaceae	France	Ellipticine	Alkaloid[43]
6.	*Brucea antidysenterica* Simaraubaceae	Africa	Bruceantin	Quassinoid[43]
7.	*Bursera microphylla* Burseraceae	Mexico	Burseran	Lignan
8.	*Campotheca acuminate* Nyssaceae	China	Campothecin	Alkaloid[43]
9.	*Catharanthus roseus* Apocynaceae	India,Africa	Vincristine, Vinblastine	Alkaloid[43]
10.	*Centaurea montata* Asteraceae	Europe	Montamine	Alkaloid
11.	*Centaurea schischkinii* Asteraceae	----------	Schischkinnin	Alkaloid
12.	*Cephalotaxus harringtonia* Cephalotaxaceae	Japan	Homoharringtonine	Alkaloid [43]
13.	*Cleistanthus collinus* Euphorbiaceae	India	Cleistanthin, Collinusin	Lignan[14]
14.	*Combretum caffrum* Combretaceae	S.Africa	Combrestatins	Stilbenes
15.\	*Croton lechleri* Euphorbiaceae	S.America	Taspine	Alkaloid
16.	*Daphne mezereum* Thymelaeaceae	Asia, Europe	Mezerein	-------
17.	*Diphylleia grayi* Berberidaceae	Japan	Diphyllin	Lignan[43]
18.	*Dysoxylum binectariferum* Meliaceae	India	Rohitukine	Alkaloid [43]
19.	*Erythroxylum pervillei* Erythroxylaceae	Madagascar	Pervilleine	Alkaloid
20.	*Euphorbia semiperfoliata* Euphorbiaceae	Europe	Jatrophane	Terpenoid [43]
21.	*Fritillaria thunbergii* Liliaceae	China,Japan	Zhebeinone	Alkaloid
22.	*Gunnera perpensa* Gunneraceae	Brazil	2-methyl-6(3-methyl 2-butenyl) benzo 1-4 quinone	Quinone
23.	*Hypericum perforatum* Clusiaceae	Europe	Hypericin	Anthraquinone
24.	*Hypoxis colchicifolia*	S.Africa	Hypoxoside, Rooperol	Glycoside

	Hypoxidaceae			
25.	*Indigofera tinctoria* Leguminosae	Asia	Indirubins	Indigoids[43]
26.	*Justicia procumbens* Acanthaceae	India	Justicidin A,B	Lignan[13]
27.	*Lantana camara* Verbenaceae	America	Verbascoside	Glucoside
28.	*Larrea tridentate* Zygophyllaceae	Mexico	Terameprocol	Lignan
29.	*Linium album* Linaceae	---------	Podophyllotoxin	Lignan
30.	*Lonicera japonica* Caprifoliaceae	Japan	Luteolin	Flavanoid
31.	*Paris polyphilla* Trilliaceae	China	Polyphyllin	
32.	*Pestemon deustus* Serophulariaceae	U.S.A	Liriodendrin	Lignan
33.	*Phaleria macrocarpa* Thymelaeaceae	Indonesia	Pinoresinol, Laricinesinol	Lignan
34.	*Podophyllum emodii* Berberidaceae	India	Epipodophyllotoxin	Alkaloid[13]
35.	*Polygonum cuspidatum* Polygonaceae	Japan,China	Resveratrol	Flavanoid
36.	*Pteris multifida* Pteridaceae	Japan	Pterokaurane	Terpenoid
37.	*Pygeum africanum* Rosacea	Africa	Amygdalin	Glycoside
38.	*Vitex rotundifolia* Verbenaceae	India, Korea	Casticin	Flavanoid
39.	*Wikstroemia viridi* Thymelaeaceae	China	Wikstromol	Caumarin

Conclusion:-

Medicinal plants maintain the health and vitality of individual and also cure various diseases including cancer without causing toxicity. Natural products discovered from medicinal plants have played an important role in treatment of cancer. In this review some anti cancer plants have been presented. These plants possess good immunomodulatry and antioxidant properties leading to anticancer activity. In conclusion this article provides the knowledge about anticancer medicinal plants of foreign origin, which are used by people all over the world. Also it is of sigsnificance to exploit novel anticancer drugs from medicinal plants. Without this early warning system, the problem of overcoming development of chemoresistance is quite considerable. In an ideal situation, therapy would be tailored to suit the individual at the outset; this is unlikely at least for the very near future, despite rapid progress in pharmacogenomics. In the meantime, a better understanding of the mechanisms of resistance will at least allow the physician to modulate the therapy on a need to do basis. Medicinal plants have contributed a rich health to human beings. Plant extracts and their bioactive compounds present in them which are responsible for anticancer activity have to be screened for their valuable information. This review had given some of the plants possessing anticancer activity for various types of cancer.

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