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Review Article

AN OVERVIEW ON POTENT HERBAL ANTICANCER DRUGS

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ABSTRACT

Cancer commonly defined as an uncontrolled growth of cells, with loss of differentiation & commonly with metastasis, spread of the cancer to other tissues and organs. Cancers are caused by smoking, addiction to liquor, chewing tobacco, imbalance diet, exposure to certain chemicals (carcinogens) etc. Mechlorethamine, Mercaptopurine, Flourouracil, Paclitaxel, Etoposide and some other are the synthetic anticancer drugs. In case of cancer treatment, more than 1000 plants have been found to possess significant anticancer properties. Chemical and biological investigations on some of these have yielded certain 'lead' molecules as nature's boon for cancer chemotherapeutic uses. With an understanding of the mechanisms of action as well as the structure activity relationship several better analogues of these lead molecules have been prepared. While the Present review deals with the herbal anticancer drugs are also stand for cancer treatment with less or no unwanted effects as compare to synthetic anticancer medicines. Some herbal anticancer drugs like ***Catharanthus roseus, Camptotheca acuminate, Podophyllum species*** and ***Taxus species*** are wildly used because of their well defined mechanism of action as anticancer drug. Proper chemical and biological investigations, understanding of the mechanisms of action, development of the structure activity relationship and high yield production by plant tissue culture of these herbal drugs promote their use against cancer as such or there semi synthetic analogues.

1. INTRODUCTION

1.1 Cancer: Cancer (a malignant growth) is medically known as neoplasm which means a relatively autonomous growth of tissues and commonly defined as an uncontrolled growth of cells, with loss of differentiation & commonly with metastasis, spread of the cancer to other tissues and organs.[1] The critical difference benign and malignant neoplasm is that benign tumour do not metasize, where as malignant tumour do.[2] A metastasis is a secondary growth originating from the primary tumour and growing elsewhere in the body.[2] Cell division is a genetic process in which a cell passes its genes onto two daughter cells, each of which is a clone or exact of itself. Sometimes, this orderly process goes wrong, the genes in a cell may suffer a mutation or some mistakes may occur in DNA replication and recombination during cell division.[3] Esophagus cancer, stomach cancer, liver cancer, colon cancer, skin cancer, breast cancer, prostate cancer and burkitt lymphoma cancer are different type of cancer.[4] Cancers are caused by smoking, addiction to liquor, chewing tobacco, imbalance diet, exposure to certain chemicals (carcinogens), infection by virus (hepatitis B and HIV) and geophysical factors.[1,3] The symptoms of cancer are including an unusual lump or swelling on the neck, armpit, abdomen, grain, testicle or breast area; a change in size; shape or colour of a mole; a sore that won't heal after several weeks; unexplained weight loss; heavy night

sweats and an unexplained pain or ache that lasts longer than four weeks.[3]

1.2 Synthetic Anti-cancer Drugs: There are number of synthetic and semi-synthetic medicines used including ***Alkylating agent*** like nitrogen mustard (Mechlorethamine, Cyclophosphamide, Chlorambucil), ethylenimine (thiotepa), alkyl sulfonate (busulfan), Nitrosoureas (carmustine, lomustine), Triazine (Dacarbazine); ***Purine antagonist*** (6-Mercaptopurine, 6-Thioguanine, fludarabine, azathioprine); ***Pyrimidine antagonist*** (5-Florouracil, Cytarabine); ***Antimetabolites*** (Folate antagonist-methotrexate); ***Antibiotics*** (Actinomycin D, Doxorubicin, Daunorubicin, Bleomycin, Mitomycin C); ***Miscellaneous*** (Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin, Imatinib, Carbaplatin); ***Semi-synthetic taxanes analogues*** (Paclitaxel, Docetaxel); ***Semi-synthetic epidophyllotoxin analogues*** (Etoposide); ***Semi-synthetic camptothecin analogues*** (Tropotecan, Irinotecan).[5,6]

With their specific action of cancerous cells they are also have number of general and specific toxicity including bone marrow depression, granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, lymphocytopenia, nausea, vomiting, diarrheoea, alopecia, amenorrhoea, teratogenesis, abortion, foetal death, hyperuricaemia, oral mucosal ulceration, intestinal denudation ulceration, generalized seizures, cerebellar ataxia, pulmonary fibrosis and many others.[5,6]

In other hand one of the most exciting discoveries within the field of plant products has been the recognition of some important herbal anticancer agents [5, 6, 7] as such and their semi-synthetic analogues[5, 6, 7] which are used in cancer treatment with less side effect and higher anticancer action. These synthetic anticancer medicines and herbal anticancer drugs are having their own specific anticancer effect on cell cycle of cancerous cells or non-phase specific effect as shown in fig1:

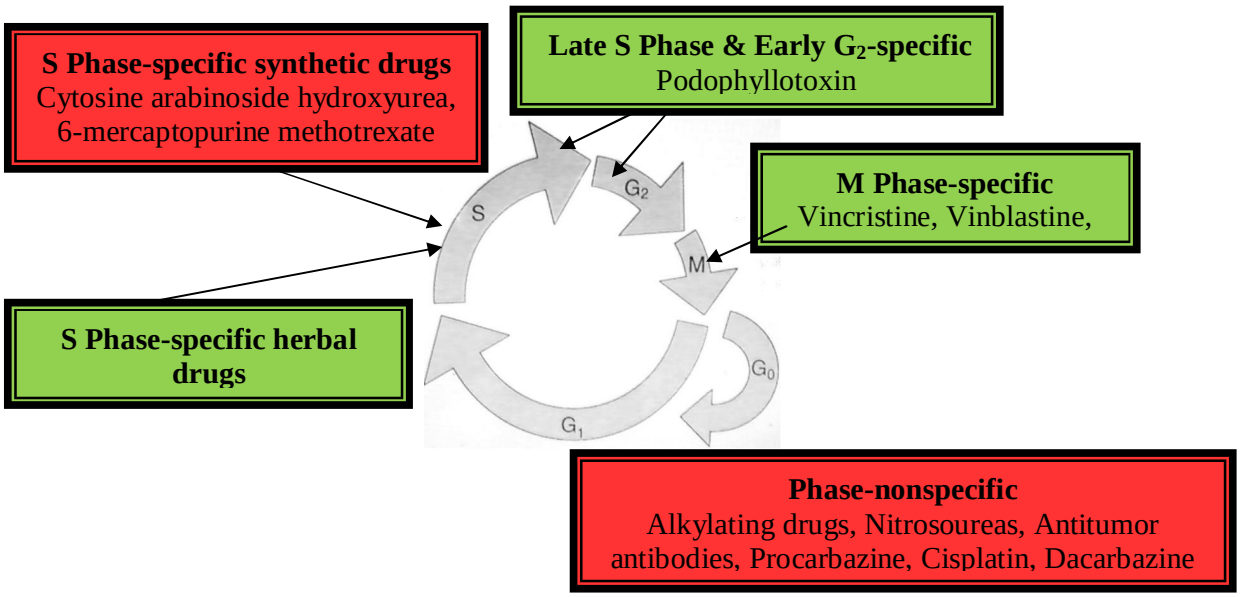

Fig.1: Cell Cycle Specific Anticancer Activity of Synthetic Medicines and Herbal Drugs

1.3 Herbal Anticancer Drugs: Plants products have been a source of medicinal agents since time immemorial. Even, today plants are the most exclusive source of drugs for the majority of world's population and plant products constitute 25% of prescribed medicines. In case of cancer treatment, more than 1000 plants have been found to possess significant anticancer properties. Chemical and biological investigations on some of these have yielded certain 'lead' molecules as nature's boon for cancer chemotherapeutic

uses. With an understanding of the mechanisms of action as well as the structure activity relationship several better analogues of these lead molecules have been prepared[8, 21]. Various herbal drugs used for treating cancer are mentioned in Table 1.

Table 1: Herbal Anticancer Drugs [9]

S. No.	Plant Source	Family	Phyto-Constituent
1.	*Catharanthus roseus*	*Apocynaceae*	Vinblastine, Vincristine
2.	*Taxus*	*Taxaceae*	Taxol
3.	*Cephalotaxus harringtonia*	*Cephalotaxaceae*	Harringtonine, Homoharringtonine
4.	*Podophyllum*	*Berberidaceae*	Podophyllotoxin, α-and β-Peltatin
5.	*Camptotheca*	*Nyssaceae*	Camptothecin
6.	*Colchicum speciosum*	*Liliaceae*	Colchicine
7.	*Ochrosia elliptica, O.moorei, O. maculate*	*Apocynaceae*	Ellipticine, 9-methoxyellipticine
8.	*Bouvardia ternifolia*	*Rubiaceae*	Bouvardin, Deoxybouvardin
9.	*Maytenus buchananii, M.serrata*	*Celastraceae*	Maytansine, Maytanacine, Maytanvaline
10.	*Tylophora crebiflora*	*Asclepiadaceae*	Tylocrebine
11.	*Fagara zanthoxyloides, F. macrophylla*	*Rutaceae*	Nitidine
12.	*Acronychia baueri*	*Rutaceae*	Acronycine
13.	*Allamanda cathartica*	*Apocynaceae*	Allamandin
14.	*Ipomoea batatas*	*Convolvulaceae*	4-ipomeanol
15.	*Penstemon deutus*	*Scrophulariaceae*	Penstimide
16.	*Baccharis megapotamica*	*Baccharin*	Compositae
17.	*Helenium autumnale*	*Compositae*	Helenalin
18.	*Liatris chapmanii*	*Compositae*	Liatrin
19.	*Phyllanthus acuminatus*	*Euphorbiaceae*	Phyllanthoside
20.	*Vernonia hymenolepis*	*Compositae*	Vernolepin
21.	*Gnidia lamprantha*	*Thymelaeaceae*	Gnidin
22.	*Jatropha gossypiifolia*	*Euphorbiaceae*	Jatrophone
23.	*Tripterygium wilfordii*	*Celastraceae*	Tripdiolide
24.	*Brucea antidysenterica*	*Simaroubaceae*	Bruceantin
25.	*Simarouba glauca*	*Simaroubaceae*	Glaucarubinone
26.	*Holacantha emoryi*	*Simaroubaceae*	Holacanthone
27.	*Marah oreganus*	*Cucurbitaceae*	Cucurbitacin
28.	*Acernegundo*	*Aceraceae*	Acer saponin P
29.	*Bersama abyssinica*	*Melianthaceae*	Hellebrigenin
30.	*Acnistus arborescens*	*Solanaceae*	Withaferin A
31.	*Combretum caffrum*	*Combretaceae*	Combretastin A-4
32.	*Steganotaenia araliaaceae*	*Umbelliferae*	Steganacin
33.	*Jacaranda caucana*	*Bignoniaceae*	Jacaranone
34.	*Stereospermum sauveolens*	*Bignoniaceae*	Lapachol
35.	*Crotalaria spectabilis*	*Leguminosae*	Monocrotaline
36.	*Heliotropium indicum*	*Boraginaceae*	Indicine-N-oxide
37.	*Cephaelis acuminate*	*Rubiaceae*	Emetine
38.	*Cyclea peltata*	*Menispermaceae*	Tetrandrine
39.	*Thalictrum dasycarpum*	*Ranunculaceae*	Thalicarpine

2. PROSPECTUS OF SOME POTENT HERBAL ANTICANCER DRUGS

2.1 *Catharanthus roseus*

2.1.1 Pharmacognosy of *Catharanthus roseus*: ***Catharanthus roseus***, commonly known as Vinca, Catharanthus, Periwinkle, Sada bahar, Sadaphul and Vinca rosea is obtained from dried whole plant of ***Catharanthus roseus*** Linn. G.Donn. family ***Apocynaceae*** and distributed in South Africa, India, U.S.A, Europe, Australia and Caribbean Islands.[7, 10, 11]

The drug is an erect, pubescent herb consists of green, simple, petiolate, ovate or oblong, unicostate, reticulate, entire, brittle leaf with acute apex and glossy appearance; violet pink-white or carmine-red, bractate, pediceellate, complete and hermaphrodite flower [11, 23] with 5 sepals, green, linear, subulate calyx, cylindrical 5 petals, rose-purple or white corolla tube and bicarpellary ovary; follicles fruits with several black seeds; also pale grey color root.[10] **Microscopically** on transverse section of leaf it shows; single layered

rectangular upper epidermis cells with unicellular covering trichomes; single layered compact elongated palisade cells; spongy parenchyma cells in intercellular spaces; collenchymas in midrib; xylem and phloem in center and cruciferous stomata on lower epidermis.[10]

Out of large number of indole alkaloids of ***Catharanthus roseus***, about 20 dimeric indole-dihydroindole alkaloids possess oncolytic activity and among them ***Vincristine*** and ***Vinblastine*** are most significant.[7, 10] Other alkaloids reported are vincoside, isovincoside (strictosidine), catharanthine, vindolinine, lochrovicine, vincolidine, ajmalicine (raubasine), reserpine, serpentine, leurosine, lochnerine, tetrahydroalstonine, vindoline, pericalline, perivine, periformyline, perividine, carosine, leurosivine, leurosidine and rovidine.[7, 10, 11] ***Vinblastine*** contains indole alkaloid part called catharanthine and dihydroindole alkaloid part called vindoline.[7, 10] The alkaloid contents in different parts show large variations as roots 0.14-1.34%, stem 0.074-0.48%, leaves 0.32-1.16%, flowers 0.005-0.84%, fruits 0.40%, seeds 0.18% and pericarp 1.14%.[11] Dry leaves contain ***Vinblastine*** (vincaleucoblastine or VLB) 0.00013-0.00063%, and ***Vincristine*** (leurocristine or LC) 0.0000003-0.0000153% which have anti-cancerous activity.[11] Structures[12] of impotent chemical constituent of vinca are following as in figure 2:

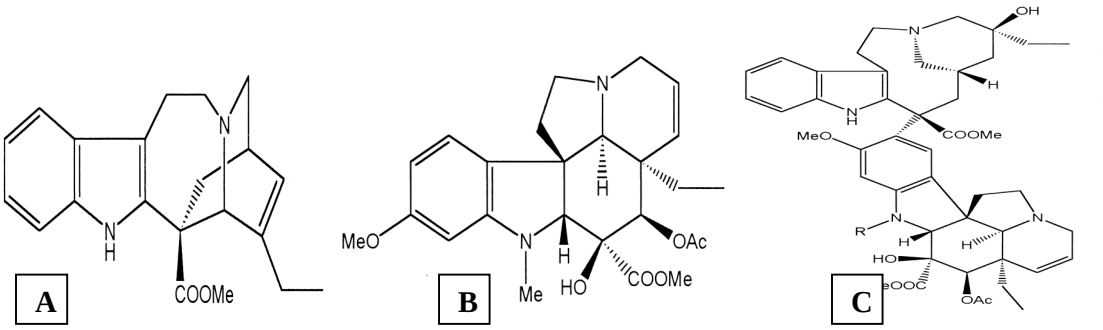

Fig. 2: "A"-Catharanthine; "B"- Vindoline, and "C"- Vincristine(R=CHO), Vinblastine(R=CH_3)

2.1.2 Pharmacology

2.1.2 Anticancer Activity of *Catharanthus roseus*: The vinca alkaloids are cell cycle–specific agents, and block cells in mitosis. The vinca alkaloids bind specifically to b-tubulin and block its ability to polymerize with a-tubulin into microtubules. In the absence of an intact mitotic spindle, duplicated chromosomes cannot align along the division plate and cell division is arrested in metaphase.[5, 6] Cells blocked in mitosis undergo changes characteristic of apoptosis. They are used for treatment of leukemias, lymphomas, and testicular cancer.[5,6,13] ***Vincristine*** is a standard component of regimens for treating pediatric leukemias, lymphomas, solid tumors, large-cell non-Hodgkin's lymphomas, and also is a standard component of regimens used to treat pediatric solid tumors such as Wilms' tumor, neuroblastoma, and rhabdomyosarcoma.[5,6] ***Vinblastine*** is employed in bladder cancer, testicular carcinomas, and Hodgkin's disease.[5, 6] Along with anticancer action vinca also have anti diabetic and antioxidant action.[13, 14]

2.2 *Camptotheca acuminate*

2.2.1 Pharmacognosy: *Camptotheca acuminta* commonly known as Cancer tree, Tree of joy and Tree of love consist of stem wood part of ***Camptotheca acuminate*** Decne, family ***Nyssaceae***; distributed in China, Tibet and indigeneous to Southern China.[7, 10, 15]

Drug consists of dark green, entire, acuminate, ovate and lanceolate leaves with 8-10 cm in length, 3-5 cm in width and reddish petiole; red colored Flowers, bitter taste.[10] Drug shows unicellular glandular trichomes on both leaf surfaces; secretary canals distributed in pith and cortex tissues near vascular tissue with gray-blank secretion product and have larger diameter in pith than in cortex tissue. Glandular trichomes also contained osmiophilic material and significantly denser

on the surfaces of young leaves than on that of old ones.[22]

All camptotheca plant parts leaves, bark, fruits and twigs contain 0.004 to 0.003% of ***Camptothecin*** as major quinoline alkaloid with other constituents like 10-Methoxy Camptothecin, 10-Hydroxy Camptothecin.[7, 10] Structures[9] of impotent chemical constituent of ***Camptotheca acuminta*** are following as in figure 3:

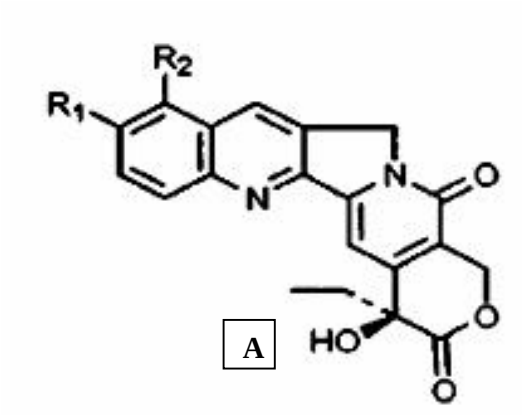

Fig. 3: "A" Basic Structure- Camptothecin (R_1 = R_2= H), 10-hydroxycamtothecin (R_1= OH, R_2=H) and 9-Aminocamptothecin (R_1= H, R_2= NH_2)

2.2.2 Anticancer Activity of *Camptotheca acuminate*: The DNA topoisomerases are nuclear enzymes that reduce torsional stress in supercoiled DNA, allowing selected regions of DNA to become sufficiently untangled to permit replication, recombination, repair, and transcription. Topoisomerase I bind covalently to double-stranded DNA through a reversible trans-esterification reaction. This reaction yields an intermediate complex and a single-strand DNA break. This "cleavable complex" allows for relaxation of the DNA torsional strain, either by passage of the intact single-strand through the nick, or by free rotation of the DNA about the noncleaved strand. Once the DNA torsional strain has been relieved, the topoisomerase I reseals the cleavage and dissociates from the newly relaxed double helix.[6]

The **Camptothecins** bind to and stabilize the normally transient DNA-topoisomerase I cleavable complex. Although the initial cleavage action of topoisomerase I is not affected, the relegation step is inhibited, leading to the accumulation of single-stranded breaks in DNA. These lesions are not by themselves toxic to the cell. However, the collision of a DNA replication fork with this cleaved strand of DNA causes an irreversible double-strand DNA break, ultimately leading to cell death. **Camptothecins** are therefore S-phase–specific drugs. This has important clinical implications, because S-phase–specific cytotoxic agents generally require prolonged exposures of tumor cells to drug concentrations above a minimum threshold to optimize therapeutic efficacy.[6]

2.3 *Podophyllum Species*

2.3.1 Pharmacognosy: ***Podophyllum*** commonly known as American mandrake, Himalayan May-Apple, is obtained from dried rhizomes and roots of plants ***Podophyllum peltatum*** Linnaeus (American podophyllum), ***Podophyllum emodi*** Wall or ***Podophyllum hexandrum*** Royle (Indian podophyllum) and ***Podophyllum pleianthum*** (Taiwanese podophyllum), ***Podophyllum delavayi***, ***Podophyllum versipelle*** belongs to family ***Berberidaceae*** and grows in eastern part of Canada, U.S.A, Virginia, Pakistan and India (Himalayas from Kashmir to Sikkim, Himachal Pradesh and some parts of Uttar Pradesh).[7, 10, 15]

Podophyllum peltatum shows subcylindrical reddish brown pieces about 5-20cm long and 5-6mm thick; Smooth (autumn rhizome) or wrinkled (summer rhizome) outer surface; enlarged nodes to from two to three times the diameter of the internodes; breaks with a short fracture and shows a starchy or horny interior; disagreeable bitter and acrid taste with slight

odour. [7, 10, 16] ***Podoophyllum hexandrum*** little resemblance to American podophyllum macroscopically shows earthy brown, hard rhizomes with about 2-4cm long and 1-2cm in diameter; much shorter internodes than in the American; Internally it is pale brown in colour and horny or starchy. It has bitter and acrid in taste with slight and characteristic odour.[7, 10, 16]
A transverse section of the rhizome shows dark coloured epidermis; thin walled polygonal, tubular cork cells; cortex and pith with large collenchymatous, parenchymatous cells; ground tissue with reddish brown resin masses, cluster calcium oxalate crystals (30-60-100μm in diameter, many exceeding 60μm), simple starch grains(3-15-25μm in diameter) and compound starch grains.[7, 10, 22]
The chief phyto-chemical constituents of the roots belong to the group of lignans, which are C18 compounds derived biosynthetically by dimerization of two C6-C3 units at the β-carbon of the side chains. The most important constituents of them are ***Podophyllotoxin***, ***β-peltatin***, and ***α-peltatin***. Some other phytoconstituents are 4'-demethyl-podophyllotoxin and its glucoside, desoxypodophyllotoxin and podophyllotoxone. Indian podophyllum contains more resin (about 6-12%) and much higher percentage of podophyllotoxin in the resin (up to 40%) than the American drug that contained only about 0.25%. β-peltatin, and α-peltatin are phytoconstituents of ***Podophyllum peltatum*** (American podophyllum).[7,10] Structures [7, 9, 10] of impotent chemical constituent of ***podophyllum Species*** are following as in figure 4:

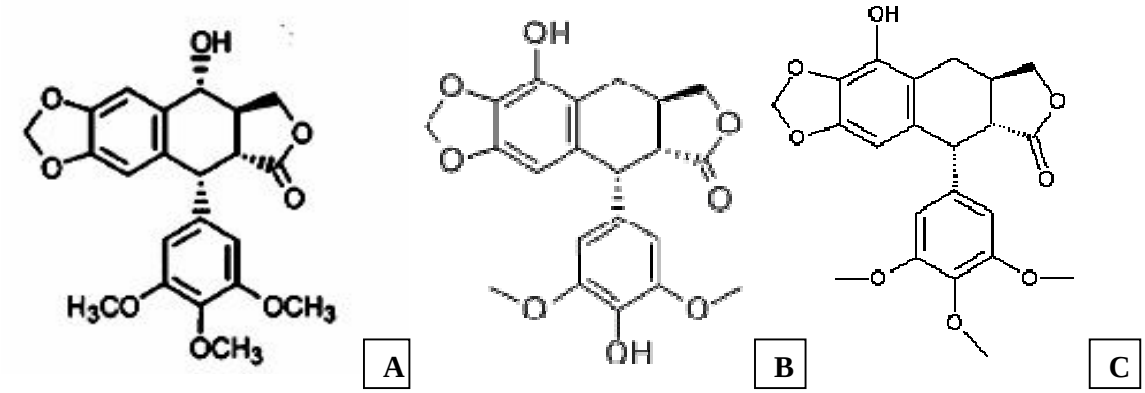

Fig. 4: "A"- Podpphyllotoxin, "B"- α-Peltatin and "C"- β-Peltatin

2.3.2 Anticancer Activity of *Podophyllum Species*: The studies of mechanism showed that their powerful antitumour properties have been attributed by either its binding to tubulin during mitosis followed by inhibiting microtubule assembly or acted by inhibiting the enzymatic activity of DNA-topoisomerase II. The mechanism of cytostatic action at the cellular level of podophyllin an inhibition of the formation of the mitotic spindle, resulting in an arrest of the cell division process in metaphase and a clumping of the chromosomes(c-mitosis). This is due to binding of **Podophyllotoxin** to tubulin, preventing these macromolecules to form microtubules, which constitute the fibers of the mitotic spindle.[17]
It is effective in the treatment of Wilms tumours, various genital tumours and in non-Hodgkin's and other lymphomas and lung cancer. **Podophyllotoxin** widely used as remedies for purgative, snake bites, periodontitis, skin disorders, coughs, various intestinal worm disease, veneral wart condyloma acuminatum, lymphadenopathy, certain tumours and in the treatment of veneral wart condyloma acuminatum.[7, 9, 10, 13]

2.4 *Taxus Species*

2.4.1 Pharmacognosy: ***Taxus*** commonly known as yew, tolispora, Himalayan yew consist of bark and roots of plants ***Taxus baccata*** L., ***Taxus bsevefolia*** Nutall, ***Taxus canadensis*** Marshall, ***Taxus cuspidata*** Sieb.et Zucc., ***Taxus florinda*** Nutallex chapman, ***Taxus globosa*** schlect, ***Taxus wallichiana*** zucc., ***Taxus fuana*** Li. Et Fu, ***Taxus mairei*** Lemee et levl, and ***Taxus chinensis*** Rehder and

obtained from China, Eastern Russia, Eastern Himalaya, Malaysia, North America, Virginia and Iowa.[7,10,18,19]

Trees or shrubs evergreen, dioecious; branchlets irregularly alternate, basal part with few or several persistent or early deciduous bud scales; winter bud scales overlapping, with prominent or indistinct, longitudinal adaxial ridges. Two-ranked, spirally arranged, sessile, or shortly petiolate leaves; two inconspicous pale gray, grayish blue, or pale yellow stomatal bands, resin canal absent. axillary, solitary reproductive structures. Pollen cones are pedicellate, globose, with overlapping bracts at base. The seeds are wrapped at least halfway by a conspicious aril, from orange to deep red in colour.[18,20]

All parts of ***Taxus*** tree contain a wide range of diterpenoid derivatives temed **Taxanes**, which are structurally related to the toxic constituents found in other ***Taxus*** species, e.g.the common yew, ***Taxus baccata***. Over a hundred **Taxanes** have been characterized from various ***Taxus*** species, and **Taxol** is a member of a small group of compounds possessing a four-membered oxetane ring and a complex ester side-chain ih their structures, both of which are essential for antilia, but in relatively low amounts(0.01-0.02%). Up to 0.033% of **Taxol** has been recorded in some samples of leaves and twigs, but generally the **Taxol** content is much laower than in bark. In all the species, with little variations, **Taxol** occurs from 0.007% to 0.01%. 50 to 150 mg of **Taxol** is obtained from 1 kg dried yew bark . Significant variation in **Taxol** content depending on season, geographical location and environmental factors as well as individual populations of trees have been noted. The content of some other **Taxane** derivatives in the bark is considerably higher, e.g. up to 0.2% baccatin III. Other **Taxane** derivatives characterized include 10-deacetyltaxol, 10-deacetylbaccatin III, cephalomannine and 10-deaceyylcephalomannine. Both baccatin III and 10-deacetylbaccatin III is readily extracted from the leaves and twigs of ***Taxus baccata*** and although the content is variable, it is generally present at much higher level (up to 0.2%) than **Taxol** can be found in ***Taxus brevefolia***.[7,10] Structure[13] of impotent chemical constituent of ***Taxus*** is following as in figure 5:

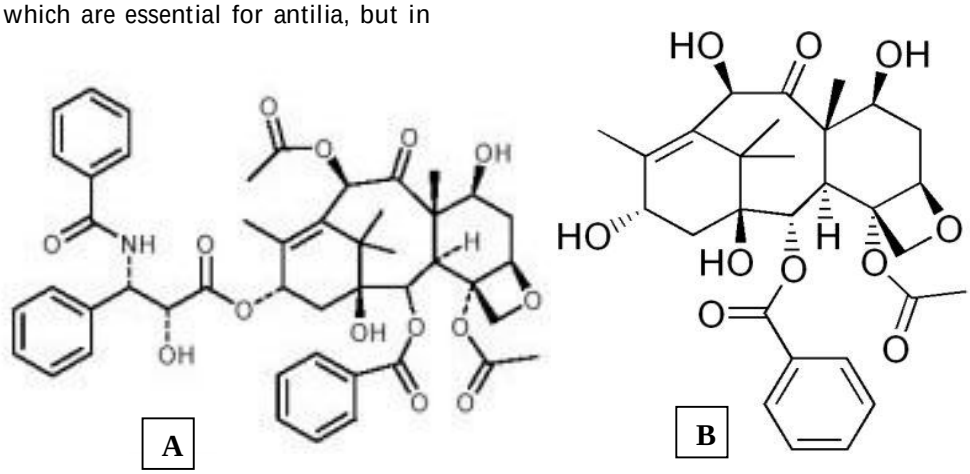

Fig. 5: "A"- Taxol, "B"- 10-deacetylbaccatin III

2.4.2 Anticancer Activity of *Taxus Species*: **Taxol** binds specifically to β-tubulin and antagonizes the disassembly of microtubules; bundles of microtubules and aberrant structures derived from microtubules appear in the M phase of the cell cycle, causing mitotic arrest. Cell killing is dependent on both drug concentration and duration of cell exposure.[5, 6] The drugs have a central role in the therapy of ovarian, breast, lung, esophageal, bladder, and head and neck cancers. Their optimal dose, schedule, and use in drug combinations still are evolving.[5, 6]

3 DISCUSSION

There is a long list of synthetic anticancer medicines which are used in cancer treatment but it is also true that these synthetic medicines have lots of unwanted effects on cancer sit as well as whole body. While our herbal anticancer drugs are also stand for cancer treatment with less or no unwanted effects as compare to synthetic anticancer medicines. Some herbal anticancer drugs like ***Catharanthus roseus, Camptotheca acuminate, Podophyllum species*** and ***Taxus species*** are wildly used because of their well defined mechanism of action as anticancer drug. Proper chemical and biological investigations, understanding of the mechanisms of action, development of the structure activity relationship and high yield production by plant tissue culture of these herbal drugs promote their use against cancer as such or there semi synthetic analogues. Further research is needed to explore more chemical modifications at various sites of the basic backbone of herbs; development of a safety, more economic and site-specific anticancer drug; development of high yield production and suitable cultivation method of anticancer plant species with higher amount of specific phyto-chemical constituents.

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