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REVIEW ARTICLE: RECENT DEVELOPMENT IN CANCER THERAPY AND ITS TREATMENT - A REVIEW

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ABSTRACT

According to the latest cancer statistics presented worldwide, there has been a dramatic increase in the rates of occurrence of some cancers, particularly in the more developed countries. Although many therapeutic strategies to prevent and/or cure this disease have been proposed and evaluated by clinicians and researchers, there remains a need to find more effective approaches. Monoclonal antibodies, that are produced in vitro, can be used in cancer treatment in a number of ways. They may enhance the immune system by reacting with certain types of cancer cells. They can be programmed to act against specific cell growth factors to interfere with the growth of cancer cells. Furthermore, they may be linked to anticancer drugs, radioactive substances, other biologic therapies, or other toxins (antibody – drug conjugates). Numerous studies have been done to find out the cure for cancer but to no avail. Herbals have been considered as efficient anticancer agents and their importance in the treatment and management of cancer cannot be overlooked. Present review is a sincere attempt to compile the most promising anticancer agents from plant origin and list their major cancer curative potentials.

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INTRODUCTION

Cancer is a disease in which the control of growth is lost in one or more cells, leading either to a solid mass of cells known as a tumour or to a liquid cancer (i.e. blood or bone marrow-related cancer). It is one of the leading causes of death throughout the world, in which the main treatments involve surgery, chemother- apy, and/or radiotherapy [1]. Chemotherapy involves the use of low-molecular-weight drugs to selectively destroy tumour cells or at least limit their proliferation. Disadvantages of many cyto- toxic agents include bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea, and the development of clinical resis- tance. These side effects occur because cytotoxic agents act on both tumour cells and healthy cells [2]. The use of chemotherapy began in the 1940s with nitrogen mustards, which are extremely power- ful alkylating agents, and antimetabolites. Since the early success of these initial treatments, a large number of additional anticancer drugs have been developed [1].

Anticancer drugs can be classified according to their mechanism of action, such as DNA-interactive agents, antimetabolites, anti-tubulin agents, molecular targeting agents, hormones, monoclonal antibodies and other biological agents [2]. In this review, the most commonly used anticancer drugs (i.e. classical cytotoxic agents) are discussed.

- Antimetabolites are one of the oldest families of anticancer drugs whose mechanism of action is based on the interaction with essential biosynthesis pathways. Structural analogues of pyrim- idine or purine are incorporated into cell components to disrupt the synthesis of nucleic acids. 5-Fluorouracil and mercaptopurine are typical pyrimidine and purine analogues, respectively. Other antimetabolites, such as methotrexate, interfere with essential enzymatic processes of metabolism.
- DNA interactive agents constitute one of the largest and most important anticancer drug families, acting through a variety of mechanisms:

· Alkylating agents lead to the alkylation of DNA bases in either the minor or major grooves. For example: dacarbazine, procar-bazine and temozolomide.
· Cross-linking agents function by binding to DNA resulting to an intra-strand or inter-strand cross-linking of DNA. Platinum complexes (e.g., cisplatin, carboplatin, oxaliplatin) and nitro- gen mustards (e.g., cyclophosphamide, ifosfamide) are the two main groups of this anticancer drug sub-family. Nitrosurea com- pounds, busulfan and thiotepa are also cross-linking agents.
· Intercalating agents act by binding between base pairs. The family include anthracyclines (e.g., doxorubicin, epirubicin), mitoxantrone and actinomycin-D.
· Topoisomerase inhibitors include irinotecan and etoposide compounds. These drugs inhibit the responsible enzymes for the cleavage, annealing, and topological state of DNA.
· DNA-cleaving agents such as bleomycin interact with DNA and cause strand scission at the binding site.
· Antitubulin agents interfere with microtubule dynamics (i.e., spindle formation or disassembly), block division of the nucleus and lead to cell death. The main members of this family include taxanes and vinca alkaloids [2].

Targeted Therapeutic Approach

The targeted or molecularly targeted therapeutic concept involves anti-cancer drugs. SMDs can penetrate the cell membrane and the blood-brain barrier more easily. They are simple organic molecules with a low molecular weight (<1000 kDa) that can be delivered orally or intravenously. To date, many of these drugs have been used as inhibitors in the treatment of cancer and other diseases.

Kinase inhibitors are a group of molecules that specifically inhibit the action of one or more protein kinases. Hence, they can be subdivided or characterized by the amino acids whose phosphorylation is inhibited [3]. The general assumption is that they block the cell signaling function, but this is only part of the whole process. It is believed that their effect is dose dependent. When high doses of kinase inhibitors are administered to patients, it has been found that they prevent kinases from linking up with the Hsp90-Cdc37 chaperone system, a complex of molecules in cells that plays a vital role in the stability of proteins [4,5]. They have been heralded as a new type of targeted therapy, because there are 400 of them under development and there are 25 already in use. A few examples are erlotinib for the treatment of non-small- cell lung cancer, lapatinib for the treatment of HER2-positive breast cancer, and sorafenib for the treatment of kidney cancer.

A second class of SMDs are the proteasome inhibitors (PIs). Interestingly, transformed cells display greater susceptibility to this kind of drug than healthy tissues [6,7]. Lactacystin was the firstthe use of a medicinal compound to block and/or minimize the growth of cancer cells. During this process the normal tissues are not affected, and this kind of treatment may be more effective and less cytotoxic than other non-targeted traditional chemotherapies. Consequently, the primary goal of targeted therapies is to fight cancer cells with greater precision and potentially fewer side effects. Small-molecule drugs (SMDs), monoclonal antibodies (moabs), antibody drug conjugates (ADCs) as well as cancer vaccines are some of the basic classified agents that are broadly used.

Cancer treatment vaccines

Cancer cure vaccines belong to the family of organic response modifiers. They are labeled as preventive (or prophylactic) vaccines and remedy (or therapeutic) vaccines. In the discipline of cancer, therapeutic vaccines are used that are both designed to treat cancers that have already developed or to stop the disease. With regard to the immune system's mode of action, it is capable of both unique and non-specific responses towards tumor cells. For a most cancers vaccine to be successful, it ought to have the capability to stimulate the immune system to act primarily in a tumor-specific fashion. In this mode, it would existing tumor antigens to immune cells and spark off CD4 (also acknowledged as helper T cells) and CD8 T cells (also regarded as cytotoxic or killer T cells). CD8 T cells when activated without delay kill tumor cells [8], whilst CD4 T cells are circuitously activated by dendritic cells and macrophages [9] to produce messengers (cytokines) that improve CD8 (killer) T-cell recreation .[10,11]

Cancer is usually classified according to the tissue from which the cancerous cells originate, the primary tumor, as well as the normal cell type they most resemble. These are location and histology, re- spectively. A definitive diagnosis usually requires the histologic ex- amination of a tissue biopsy specimen by a pathologist, although the initial indication of malignancy can be symptoms or radio- graphic imaging abnormalities. Most cancers can be treated and some cured, depending on the specific type, location, and stage. Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy. As research develops, treatments are becoming more specific for different varieties of cancer. There has been significant progress in the development of targeted therapy drugs that act specifically on detectable molecu- lar abnormalities in certain tumors, and which minimize damage to normal cells. The prognosis of cancer patients is most influ- enced by the type of cancer, as well as the stage, or extent of the disease. In addition, histologic grading and the presence of specific molecular markers can also be useful in establishing prog- nosis, as well as in determining individual treatments.

Development of Anticancer Drugs from Plants

It is estimated that there are roughly 500,000 higher flowering plant species occupying terrestrial habitats. A large number of species have only been very superficially examined for their phar- macological and medical application. Less than 1% of these spe- cies has been thoroughly investigated for their potential use as novel therapeutic agents.

Traditionally, cancer drugs were discovered through large-scale screening of synthetic chemicals against animal tumor systems, primarily murine leukemia's. The agents discovered in the first two decades of cancer chemotherapy (1950-1970) largely interacted with the DNA or its precursors, inhibiting the synthesis of new genetic material or causing irreparable damage to DNA itself. In the area of cancer treatment, many claims have been made for the beneficial effects of plants [12].

Drug discovery from medicinal plants has played an important role in the treatment of cancer. Of all available anticancer drugs between 1940 and 2002, 40% were natural products per se or nat- ural product-derived with another 8% considered natural product mimics [13].

Epipodophyllotoxins

In the development of the anticancer drugs, etoposide, and teni- poside, as semi synthetic derivatives of epipodophyllotoxins were isolated from Podophyllum peltatum L. and Podophyllum emodi. [14]. Po- dophyllum peltatum is most commonly known as the mayapple, but in various regions it is also known as Devil's apple, hog apple, In- dian apple, umbrella plant, wild lemon, and American mandrake. Podophyllotoxin, extracted from the mandrake plant (may-apple; Podophyllum peltatum L.) was used as a folk remedy by the American Indians and early colonists for its emetic, cathartic and anthel- mintic effects. The mayapple is a perennial plant in the barberry family (Berberidaceae), which is found in woodlands in Canada and the Eastern U.S. The two-leaved plants normally produce a single, small white flower (usually in May, thus the name) from the fork in the stem. The flower develops into a pulpy, lemon yellow berry, which ripens in late summer and is the only part of the plant that isn't poisonous. The plant's long, thin rhizome (a hori- zontal underground stem from which the roots grow) is the most poisonous part, but also the most useful because it contains high concentrations of the compounds podophyllotoxin and alpha and beta peltatin, all of which have anticancer properties. Podophyllo- toxin (podofilox) and its derivatives, etoposide and teniposide, are all cytostatic (antimitotic) glucosides. Podofilox, an extract of the mayapple generally acts as a cell poison, to which cells undergo- ing mitosis (division) are particularly vulnerable. Podophyllotoxin binds to tubulin at a site distinct from that for interaction with the vinca alkaloids. Etoposide and teniposide have no effect on microtubular structure or function at usual concentrations [15,16].

Currently, extracts of the plant are used in topical medications for genital warts that are caused by the human papilloma virus (HPV), and some skin cancers. The purgative action of mayapple rhizome powder is very strong, and the compounds in it are too toxic to attempt self-medication with this plant. The FDA rates the use of this plant as "unsafe."

Paclitaxel

Taxus baccata and Taxus brevifolia are members of the yew family (Taxaceae). T. baccata is commonly known as the English yew. T. brevifolia is most commonly known as the Pacific Yew, but it may also be referred to as the Western or American yew. The FDA designated it the only approved source of paclitaxel (Taxol), an anticancer drug that has gained a lot of attention. The bright red fruits of yews are called arils and each cups a single seed. The arils, which are moderately sweet, are the only parts of the plant that do not contain poisonous alkaloids called taxines.

Paclitaxel's anticancer properties were first discovered in the 1960s as a result of a huge plant-screening program initiated by the National Cancer Institute (NCI). Researchers further identi- fied its specific functions (it keeps fiber-like cell structures called microtubules from breaking down) in 1979, and clinical trials to test its safety started in 1983. The compound has been identi- fied in lesser quantities in other yew species such as the American yew and T. cuspidata, the Japanese Yew. The English yew contains a similar compound called docetaxel, which is marketed under the name Taxotere. The development of paclitaxel firstly isolated from the bark of western yew tree in 1971 has proved an effective drug for the treatment of breast and ovarian cancers [17].

Paclitaxel, which is sold as Taxol by Bristol-Myers Squibb, binds to microtubules and inhibits their depolymerization (molecular disassembly) into tubulin [18, 19]. This means that paclitaxel blocks a cell's ability to break down the mitotic spindle during mitosis (cell division). With the spindle still in place the cell can't divide into daughter cells (this is in contrast to drugs like colchicine and the Vinca alkaloids, which block mitosis by keeping the spindle from being formed in the first place). Paclitaxel is given intrave- nously (it irritates skin and mucous membranes on contact), and is most effective against ovarian carcinomas and advanced breast carcinomas.

Docetaxel

Rhone-Poulenc Rorer has trademarked Docetaxel as Taxotere. Like paclitaxel, it prevents the mitotic spindle from being broken down by stabilizing the microtubule bundles, but clinical trials in- dicate that it is about twice as effective as paclitaxel in doing so. Docetaxel, which is also given intravenously, is being tested on carcinomas of the bladder, cervix, lung, and ovaries, on malignant melanoma and on non-Hodgkin's lymphoma.

Beta-lapachone and Lapachol

A quinone is derived from lapachol (a naphthoquinone), which can be isolated from the lapacho tree (Tabebuia avellanedae), a mem- ber of the catalpa family (Bignoniaceae). Like camptothecin and topotecan, ß-lapachone inhibits DNA topoisomerase I.

Researchers have found that this compound has promising anti- cancer and antiviral properties. Topoisomerase inhibitors, includ- ing beta-lapachone, seem to be effective against several types of cancer, including lung, breast, colon and prostate cancers and malignant melanoma. The use of beta-lapachone in humans has been limited due to its toxicity. However, 3-allyl-beta-lapachone has been found to have lower toxicity in cell culture tests, and therefore may prove to be more useful than beta-lapachone.

Beta-lapachone works by disrupting DNA replication. Topoi- somerase I is an enzyme that unwinds the DNA that makes up the chromosomes. The chromosomes must be unwound in order for the cell to use the genetic information to synthesize proteins. Be- ta-lapachone keeps the chromosomes wound tight, and so the cell can't make proteins. As a result, the cell stops growing. Because cancer cells grow and reproduce at a much faster rate than normal cells, they are more vulnerable to topoisomerase inhibition than are normal cells. Beta-lapachone also interferes with the replica- tion of HIV-1, thereby slowing the advancement of the disease.

Colchicine

It is a water-soluble alkaloid found in the autumn crocus that blocks or suppresses cell division by inhibiting mitosis. Specifi- cally, it inhibits the development of spindles as the nuclei are di- viding. Normally, the cell would use its spindle fibers to line up its chromosomes, make a copy of them, and divide into two new cells with each daughter cell having a single set of chromosomes. With colchicine present, the spindle fibers don't form, and so the cell can't move its chromosomes around. The cell may end up copying some or all of the chromosomes anyway, but can't parcel them out into new cells, and so it never divides. Because cancer cells divide much more rapidly than normal cells, cancers are more susceptible to being poisoned by mitotic inhibitors such as colchicine, paclitaxel, and the Vinca alkaloids, vincristine and vinblastine.

Vincristine and Vinblastine

Vinca alkaloids are obtained from the Madagascar periwinkle plant. They are naturally occurring or semi synthetic nitrogenous bases extracted from the pink periwinkle plant Catharanthus ro- seus G. Don. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine and vindesine (VDS), but only VCR, VBL and VRL are approved for use in the United States.

The main mechanisms of vinca alkaloid cytotoxicity is due to their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle ap- paratus, directly causing metaphase arrest. However, they can do many other biochemical activities that may or may not be related to their effects on microtubules. Many of the effects that do not include microtubule interruption happen only after treatment of cells with clinically irrelevant doses of the vinca alkaloids. Never- theless, the vinca alkaloids and other antimicrotubule agents also have an effect on both nonmalignant and malignant cells in the nonmitotic cell cycle, because microtubules are involved in many nonmitotic functions.

The vinca alkaloids connect to binding sites on tubulin that they are separate from those of the taxanes, colchicine, podophyllo- toxin and guanosine 5’ triphosphate. Binding occurs rapidly and can reverse too. Existing evidence maintains the existence of two vinca alkaloid binding sites per mole of tubulin dimer [20].

Developments Towards Newer Anticancer Agents

In the early development of modern medicine, biologically ac- tive compounds from higher plants have played a vital role in providing medicines to combat pain and diseases. For example, the organic monographs of British Pharmacopoeia of 1932 had more than 70% plant-derived products. However, with the advent of synthetic medicinal chemistry, the role of plant derived thera- peutic agents significantly declined (mostly) in the economically developed nations. The synthetic drugs are more toxic to animal body. Besides curing cancer, they harm the normal cells of the body and are producing severe side effects that are not only long living but may pose threat to patient’s life.

Ganoderma lucidum, commonly referred to as Lingzhi in Japan or Reishi in China, has been used in Asia for health promotion for centuries. It is considered to be a natural medicine that promotes longevity and maintains the vitality of human beings. Its ben- eficial clinical effects in patients with hepatitis, hyperglycemia, chronic bronchitis, cancer, muscular dystrophy, arteriosclerosis, hypertension, hypercholesterolemia, and leukopenia have been confirmed in pharmacologic studies in recent years. The fruiting bodies, mycelia, and spores have recently received more and more attention not only as home remedies but also as new drug sources [22, 23]. The anti-cancer effects of G. lucidum have been dem- onstrated in both in vitro [24] and in vivo studies. In addition, the observed anti-cancer activities of Ganoderma have prompted its usage by cancer patients alongside chemotherapy [25]. The useful- ness of Ganoderma in benign prostatic hyperplasia has already been reported in rat models [26].

Sphaeranthus indicus (Compositae) is an herb found mostly in south- ern India. It is bitter stomachic, stimulant, alterative, pectoral, demulcent, and external emollient. The herb is an ingredient of- certain proprietary marketed preparations in India, namely, “Pros- tabliss” used for the management of benign prostatic hyperplasia. Nahata et al., (2013) screened S. indicus, Ganoderma

lucidum and Urtica dioica for their cytotoxicity against human cancer cell lines and found S. indicus to be the most effective in inhibiting the pro- liferation of prostate cancer cell lines, that is, PC-3 and DU-145. The petroleum ether, ethanol and aqueous extracts of the test drugs were screened for their in vitro cytotoxicity. S. indicus proved to be the best in these studies and its petroleum ether extract exhibited inhibitory activity against most of the human cancer cell lines, namely, lung (A549), prostate (PC-3 andDU-145), colon (Colo-205), neuroblastoma (IMR-32), and breast cancer (MCF-7). It was concluded that S. indicus induces apoptosis through mito- chondrial-dependent pathway in HL-60 Cells and exerts cytotoxic potential on several human cancer cell lines [21]. Sphaeranthus indi- cus and Urtica dioica have already been reported for their usefulness in benign prostatic hyperplasia [27, 28].

The Chinese herbal medicine Radix sophorae is widely applied as an anti-carcinogenic/anti-metastatic agent against liver cancer. Cheung et al., (2007) showed that Leachianone A, isolated from Radix sophorae, possessed a profound cytotoxic activity against hu- man hepatoma cell line HepG2 in vitro, with an IC50 value of 3.4 mg/ml post-48-h treatment. Its mechanism of action involved both extrinsic and intrinsic pathways of apoptosis. Its anti-tumor
effect was further demonstrated in vivo by 17–54% reduction of tumor size in HepG2-bearing nude mice, in which no toxicity to the heart and liver tissues was observed. In conclusion, this is the first report describing the isolation of Leachianone A from Radix sophorae and the molecular mechanism of its anti-proliferative ef- fect on HepG2 cells [29].

The pomegranate tree, Punica granatum, especially its fruit, pos- sesses a vast ethnomedical history and represents a phytochemi- cal reservoir of heuristic medicinal value. The tree/fruit can be divided into several anatomical compartments: seed, juice, peel, leaf, flower, bark and roots, each of which has interesting phar- macologic activity. Juice and peels, for example, possess potent antioxidant properties, while juice, peel and oil are all weakly es- trogenic and heuristically of interest for the treatment of meno- pausal symptoms and sequelae. The use of juice, peel and oil has also been shown to possess anticancer activities, including inter- ference with tumor cell proliferation, cell cycle, invasion and an- giogenesis [30].

Betulinic acid, a pentacyclic triterpene, is a common secondary metabolite of plants, primarily from Betula species (Betulaceae). Pisha et al., (1995) extracted Ziziphus mauritiana Lam. (Rham- naceae) collected in Zimbabwe. The ethyl acetate- soluble extract displayed selective cytotoxicity against human melanoma cells (MEL-2). Betulinic acid was then found to be active in vivo us- ing athymic mice carrying human melanomas, with little toxicity. Further biological studies indicated that betulinic acid works by induction of apoptosis [31]. Pre-clinical development towards a topical formulation is also ongoing.

Turmeric has been shown to possess variety of pharmacologi- cal properties such as anti-inflammatory, anti-carcinogenic and anti-oxidant by different workers. Yasmin et al., (1998) have re- ported that turmeric also activates the lymphocytes and induces apoptosis of tumor cells [32]. Spectrofluorimetric determination can now be carried out for curcumin in any formulation or drug mixtures [33].

The antitumor activity of the methanolic extract of Glinus lotoides has been evaluated against Dalton's ascitic lymphoma (DAL) in Swiss albino mice. A significant enhancement of mean survival time of tumor bearing mice and peritoneal cell count in normal mice was observed with respect to the control group [34].

Andrographolide, the major diterpenoid of the Andrographis pan- iculata extract has shown cytotoxic activity against KB (human epidermoid carcinoma) and P-388 (lymphocytic leukemia) cells. The methanol extract of aerial parts of Andrographis paniculata and some of the isolated compounds showed growth inhibitory and differentiating activity on M1 (mouse myeloid leukemia) cells [35].

β-hydroxyisovalerylshikonin (HIVS), which was isolated from the plant Lithospermum radix (roots of Lithospermum erythrorhizon) induces apoptosis in various cell lines of human tumor cells. Suppression of the activity of PLK-1 (polo-like kinase 1) via in- hibition of tyrosine kinase activity by β- HIVS might play an im- portant role in the induction of apoptosis [36].

Bioassay directed fractionation of Saussurea lappa led to the isola- tion of a novel lappadilactone and seven sesquiterpene lactones as cytotoxic principles against selected human cancer cell lines. Lap-padilactone, dehydrocostus lactone, and costunolide exhibited the most potent cytotoxicity against Hep-G2, OVCAR-3 and HeLa cell lines [37].

Litchi fruit pericarp (LFP) extract contains significant amounts of polyphenolic compounds and exhibits powerful antioxidative activity against fat oxidation in vitro. This study confirmed the an- ticancer activity of LFP extract on human breast cancer in vitro and in vivo, and elucidated the mechanism of its activity [38]. An isolate "CD lignan mixture" comprising lignans from stem wood of Cedrus deodara consisting of (-)-wikstromol (75 - 79 %), (-)-matairesinol (9 - 13 %) and benzyl butyrolactol (7 - 11 %) was studied for its in vitro cytotoxicity against human cancer cell lines. The in vivo anticancer activity of CD lignan mixture was studied using Ehrlich ascites carcinoma and colon carcinoma (CA-51) models in mice [39]. The tumor regression observed with Ehrlich ascites carcinoma and CA-51 was 53 % and 54 %, respectively, when CD lignan mixture was given at 300 mg/kg, i.p. for nine days in the Ehrlich ascites carcinoma bearing mice and 400 mg/ kg, i.p. for the same period in the CA-51 model. It was compara- ble with 5-fluorouracil at 22 mg/kg and 20 mg/kg, respectively. Pine needles (Pinus densiflora Siebold et Zuccarini) have long been used as a traditional health-promoting medicinal food in Korea. To investigate their potential anticancer effects, antioxidant, an- timutagenic, and antitumor activities were assessed in vitro and/ or in vivo by Kwak et al., (2006). PNE exposure effectively in- hibited the growth of cancer cells (MCF-7, SNU-638, and HL-60) compared with normal cell (HDF) in 3-(4, 5-dimethylthiazol- 2-yl)- 2, 5-diphenyltetrazolium bromide assay. In in-vivo antitumor studies, freeze-dried pine needle powder supplemented (5%, wt/ wt) diet was fed to mice inoculated with Sarcoma-180 cells or rats treated with mammary carcinogen, 7, 12-dimethylbenz [a] anthracene (DMBA, 50 mg/kg body weight). Tumorigenesis was suppressed by pine needle supplementation in the two model sys- tems. Moreover, blood urea nitrogen and aspartate aminotrans- ferase levels were significantly lower in pine needle-supplemented rats in the DMBA-induced mammary tumor model. These results demonstrated that pine needles exhibit strong antioxidant, anti- mutagenic, and antiproliferative effects on cancer cells and also antitumor effects in vivo and point to their potential usefulness in cancer prevention [40].Polyalthia longifolia is a lofty evergreen tree found in India and Sri Lanka. We are reporting first time the anticancer potential of

P. longifolia leaves extract (A001) and its chloroform fraction (F002). Both inhibited cell proliferation of various human cancer cell lines in which colon cancer cells SW-620 showed maximum in- hibition with IC50 value 6.1 µg/ml. Furthermore, F002 induce apoptosis in human leukemia HL-60 cells as measured by several biological end points. F002 induce apoptotic bodies formation, DNA ladder, enhanced annexin-V-FITC binding of the cells, in- creased sub-G0 DNA fraction, loss of mitochondrial membrane potential (ΔΨmt), release of cytochrome c, activation of caspase-9, caspase-3, and cleavage of poly ADP ribose polymerase (PARP) in HL-60 cells. All the above parameters revealed that F002-in- duced apoptosis through the mitochondrial-dependent pathway in HL-60 cells [41].Ashwagandha is regarded as a wonder shrub of India and is com- monly used in Ayurvedic medicine and health tonics that claim its variety of health-promoting effects. Surprisingly, these claims are not well supported by adequate studies, and the molecular mecha- nisms of its action remain largely unexplored to date. Widodo et al., (2007), undertook a study to identify and characterize the antitumor activity of the leaf extract of ashwagandha. Selective tumor-inhibitory activity of the leaf extract (i-Extract) was identi- fied by in vivo tumor formation assays in nude mice and by in vitro growth assays of normal and human transformed cells [42].

Table 1.Current status of marine natural products in anticancer preclinical or clinical trials [43,44].

Compound (figure number)	Source organism	Chemical class	Molecular target	Current status
Ecteinascidin 743	Ecteinascidia turbinate (tunicate; possible bacterial source)	Tetrahydroisoquinolone alkaloid	Tubulin	Phase II
Dolastatin 10	Dolabella auricularia /Symploca sp. (mollusc/cyanobacterium)	Linear peptide	Tubulin	Phase II
Bryostatin 1	Bugula neritina (bryozoan)	Macrocyclic lactone	PKC	Phase II
Synthadotin	Dolabella auricularia /Symploca sp. (synthetic analogue)	Linear peptide	Tubulin	Phase II
dolastatin 15 derivative)				
Kahalalide F	Elysia rufescens/Bryopsis sp. (mollusc/green alga)	Cyclic depsipeptide	Lysosomes/erbB pathway	Phase II
Squalamine	Squalus acanthias (shark)	Aminosteroid	Phosopholipid bilayer	Phase II
Dehydrodidemnin B	Tridemnum solidum	Cyclic depsipeptide	Ornithine	Phase II
Aplidine)	(tunicate, synthetic; possible bacterial/cyanobacterial source)		decarboxylase	
Didemnin B	Tridemnum solidum (tunicate)	Cyclic depsipeptide	FK-506 bp	Phase II (discontinued)
Cemadotin	Dolabella auricularia /Symploca sp.	Linear peptide	Tubulin	Phase II
dolastatin	(synthetic analogue)			(discontinued)
15 derivative)				
Soblidotin -	Dolabella auricularia /Symploca sp.	Linear peptide	Tubulin	Phase I
dolastatin 10 derivative)	(synthetic analogue)			
halichondrin	Halichondria okadai	Macrocyclic	Tubulin	Phase I
B derivative)	(sponge, synthetic)	polyether		
	Psammaplysilla sp.	Indolic cinnamyl	HDAC/DNMT	Phase I
Psammaplin derivative)	(sponge, synthetic)	hydroxamate		
Discodermolide	Discodermia dissolute (sponge)	Lactone	Tubulin	Phase I
	Cymbastella sp.	Linear peptide	Tubulin	Phase I
(Hemiasterlin derivative)	(synthetic analogue of sponge metabolite)			
	Jaspis digonoxea	q-Lactam peptide	Methionine	Phase I
(Bengamide B derivative)	(sponge, synthetic)	derivative	aminopeptidase	
	Agelas mauritianus	a-Galacosylceramide	Va24 + NKT cell	Phase I
(Agelasphin derivative)	(sponge, synthetic)		activation	
Curacin A	Lyngbya majuscula	Thiazole lipid	Tubulin	Preclinical

CONCLUSION

Among the foremost common cancer therapies like therapy, radiotherapy and surgery, the on top of mentioned treatment approaches area unit tools to prognose, diagnose, or treat cancer. The end result of a number of them area unit product that area unit in development or are authorized by the federal agency to be utilized in clinical practise. lastly, though such new generation of cancer treatment is related to many adverse effects, like skin condition rash, internal organ disfunction, thrombosis, cardiovascular disease, and albuminuria, these targeted therapies (immunophenotyping, neoplasm genomics) were proved to usually be higher tolerated than ancient therapy. They need additionally proved to scale back the general survival and improve the quality of living of cancer patient. In recent years, appreciable attention has been targeted on identi- fying present substances capable of inhibiting, retard- ing, or reversing the method of time period carcinogenesis. malignant neoplasm drug having low aspect effects, causation necrobiosis and target specific toxicity to the cancer cells area unit medicine of selection.

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