International Journal of Phytomedicine 3 (2011) 09-26
http://www.arjournals.org/index.php/ijpm/index

Review

ISSN: 0975-0185

Natural sources as potential anti-cancer agents: A review

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Abstract

Natural products remain an important source of new drugs, new drug leads and new chemical entities. The plant based drug discovery resulted mainly in the development of anticancer agents including plants (vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan and irinotecan), marine organisms (citarabine, aplidine and dolastatin 10) and micro-organisms (dactinomycin, bleomycin and doxorubicin). Beside this there is numerous agents identified from fruits and vegetables can used in anticancer therapy. The agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green tea), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), beta carotene (carrots), and dietary fiber. In this review active principle derived from natural products are offering a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel lead compound and potentially relevant mechanisms of action.

Keywords: Cancer, vincristin, vinblastin, fruit, vegetables.

Introduction

Cancer continues to be one of the major causes of death worldwide and only modest progress has been made in reducing the morbidity and mortality of this disease [1]. Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment. As many as 95% of all cancers are caused by life style and may take as long as 20–30 years to develop. Current estimates from the American Cancer Society and from the International Union Against Cancer indicate that 12 million cases of cancer were diagnosed last year, with 7 million deaths worldwide; these numbers are expected to double by 2030 (27 million cases with 17 million deaths) [2].

According to a report of World Health Organization, more than 80% of world's populations depend on traditional medicine for their primary health care needs [3,4]. Plants have a long history of use in the treatment of cancer and it is significant that over 60% of currently used anti-cancer agents are come from natural sources [5]. Naturally occurring drugs that are part of the war against cancer include vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivative (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and others. In fact, half

of all anti-cancer drugs approved internationally were either natural products or their derivatives and were developed on the basis of knowledge gained from small molecules or macromolecules that exist in nature [6,7]. In between 2001 and 2005, 23 new drugs derived from natural products were introduced for the treatment of disorders such as bacterial and fungal infections, cancer, diabetes, dyslipidemia, atopic dermatitis, Alzheimer's disease and genetic diseases such as tyrosinaemia and Gaucher disease out of these 4 drugs have been approved as anti cancer agents. The approved anti cancer agents in 2002 doxorubicin, in 2002 estradiol, in 2004 cholorophyll and l- aspartic acid and taxol nanoparticles in 2005 [8]. Three new drugs also introduced in 2007 originate from microbial sources for the treatment of cancer is marine alkaloid trabectedin, epothilone derivative ixabepilone and temsirolimus [9].

Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organisms and microorganisms as potential anti-cancer agent [10,11]. In this present study the potential anti-cancer agent from plants, marines, microorganisms and dietary (fruits, vegetables, and spices) sources with some recent advancement in the field of cancer research were discussed.

Plants as source of anti-cancer agents:

The history of plant as source of anti-cancer agents started in earnest in the 1950s with the discovery and development of the vinca alkaloids (vinblastine and vincristine) and the isolation of the cytotoxic podophyllotoxins. Vinca alkaloid was responsible for an increase in the cure rates for Hodgkin's disease and some forms of leukemia [12]. Vincristine inhibits microtubule assembly, inducing tubulin self-association into coiled spiral aggregates [13]. Etoposide is a epipodophyllotoxin, derived from the mandrake plant Podophyllum peltatum and the wild chervil Podophyllum emodi [14]. It has also significant activity against small-cell lung carcinoma [15]. Etoposide is a topoisomerase II inhibitor, stabilizing enzyme–DNA cleavable complexes leading to DNA breaks [16]. The taxanes paclitaxel and docetaxel has been show antitumor activity against breast, ovarian and other tumor types in the clinic trial. Paclitaxel stabilizes microtubules and leading to mitotic arrest [17]. In addition, the camptothecin derivatives irinotecan and topotecan, have shown significant antitumor activity against colorectal and ovarian cancer respectively [18,19]. These compounds were initially obtained from the bark and wood of Nyssacea Camptotheca accuminata and act by inhibiting topoisomerase I [20]. The taxanes and the camptothecins are presently approved for human use in various countries (Table 1).

Table 1: Plant based anticancer agents in clinical practice.

S.No.	Compound	Uses	Status
1.	Vincristine	Leukemia, lymphoma, breast, lung, pediatric solid cancers and others	Phase III/IV
2.	Vinblastine	Breast, lymphoma, germ-cell and renal cancer	Phase III/IV
3.	Paclitaxel	Ovary, breast, lung, bladder and head and neck cancer	Phase III/IV
4.	Docetaxel	Breast and lung cancer	Phase III
5.	Topotecan	Ovarian, lung and pediatric cancer	Phase II/III
6.	Irinotecan	Colorectal and lung cancer	Phase II/III

Rohitukine the plant alkaloid, isolated from the leaves and stems of Dysoxylum binectariferum (Maliaceae) [21,22]. Synthetic flavone derived from rohitukine, Flavopiridol representing the first cyclin-dependent kinase inhibitor to enter the clinical trial [23]. The mechanism of action involves interfering with the phosphorylation of cyclin-dependent kinases and arrest cell-cycle progression at growth phase G1 or G2 [24,25].

Homoharringtonine an alkaloid isolated from the Chinese tree Cephalotaxus harringtonia (Cephalotaxacea) [26]. The mechanism of action is the inhibition of protein synthesis and blocking cell-cycle progression [27]. It has shown efficacy against various leukemias [28]. A lung-cancer-specific antineoplastic agent 4-Ipomeanol is isolated from the sweet potato Ipomoea batata (Convolvulaceae) [29]. The mechanism of action is converted into DNA-binding metabolites upon metabolic activation by cytochrome P450 enzymes that are present in cells of the lung [30]. DNA topoisomerase I inhibitor β-lapachone, that induces cell-cycle delay at G1 or S (synthesis) phase before inducing either apoptotic or necrotic cell death in a variety of human carcinoma cells, including ovary, colon, lung, prostate and breast [31].

Beside this there are so many plants which are used in cancer; following enlist the plant which prevent and target for future studies as potential anticancer agent (Table 2):

Table 2: Plants used as anti-cancer.

S.No	Plant Species	Family	Plant Part	References
1.	Salvia officinalis	Labiatae	Leaves	[32]
2.	Viscum album	Loranthaceae	Leaves	[33]
3.	Combretum caffrum	Combretaceae	Bark	[34]
4.	Melaleuca alternifolia	Myrtaceae	Leaves	[35]
5.	Lavandula angustifolia	Labiatae	Leaves	[35]
6.	Aglaia foveolata	Meliaceae	Fruit	[36]
7.	Maytenus serrata	Celastraceae	Seed	[37]
8.	Tabebuia impetiginosa	Bignoniaceae	Stem bark and trunk wood	[38,39]
9.	Tabebuia rosea	Bignoniaceae	Stem bark and trunk wood	[38,39]
10.	Tabebuia serratifolia	Bignoniaceae	Stem bark and trunk wood	[38,39]
11.	Dipteryx odorata	Fabaceae	Seed	[40]
12.	Thapsia garganica	Apiaceae	Fruit	[41]
13.	Indigofera tinctoria	Leguminosae	Aerial part	[42]
14.	Matricaria chamomilla	Asteraceae	Flower	[43]
15.	Erythroxylum pervillei	Erythroxylaceae	Root	[44]
16.	Broussonetia papyrifera	Urticaceae	Entire	[45]
17.	Cyclopia intermedia	Fabaceae	Leaves	[46]
18.	Scutellariae radix, Scutellariae indica	Labiatae	Root	[47]
19.	Physalis philadelphica	Solanaceae	Seed	[48]
20.	Dysoxylum binectariferum	Meliaceae	Stem bark	[49]
21.	Aristotelia chilensis	Elaeocarpaceae	Leaf and Stem	[50]
22.	Cyathostemma argentium	Annonaceae	Root	[51]
23.	Epimedium hunanense	Berberidaceae	Aerial parts	[52]
24.	Croton urucurama	Euphorbiacaeae	Bark	[53]
25.	Epilobium hirsutum	Onagraceae	Entire	[54]
26.	Pleione bulbocodioides	Orchidaceae	Tuber	[55]
27.	Cassia quinquangulata	Caesalpiniaceae	Root	[56]
28.	Begonia glabra	Begoniaceae	Entire	[57]
29.	Celastrus orbiculatus	Celastraceae	Entire	[57]
30.	Croton draco	Euphorbiacaeae	Aerial parts	[57]
31.	Smilax sieboldii	Liliaceae	Entire	[58]
32.	Ximenia Americana	Olacaceae	Root	[58]

33.	Maytenus emarginata	Celastraceae	Entire	[59]
34.	Sarcandra glabra	Choranthaceae	Entire	[60]
35.	Salvia plebeian	Labiatae	Aerial	[61]
36.	Scutellaria barbata	Labiatae	Entire	[62]
37.	Ocotea caparrapi	Lauraceae	Essential oil	[63]
38.	Caragana cuneata	Leguminosae	Leaf	[64]
39.	Croton flavens	Euphorbiacaeae	Leaf	[65]
40.	Euphorbia heterophylla	Euphorbiacaeae	Stem	[65]
41.	Echites vucatanensis	Apocynaceae	Latex	[65]
42.	Thevetia ahouia	Apocynaceae	Leaf and Stem	[65]
43	Thevetia gaumeri	Apocynaceae	Leaf and Stem	[65]
44.	Thevetia peruciana	Apocynaceae	Leaf and Stem	[65]
45.	Euphorbia ebracteolata	Euphorbiacaeae	Aerial parts	[66]
46.	Dioscorea collettii	Dioscoreaceae	Rhizome	[67]
47.	Juglans mandshurica	Juglandaceae	Root	[68]
48.	Maackia tenuifolia	Leguminosae	Root	[69]
49	Juncus acutus	Juncaceae	Leaf	[70]
50.	Hedyotis chrysotricha	Rubiaceae	Entire	[71]
51.	Arisaema erubescens	Araceae	Root	[72]
52.	Leptadenia hastate	Asclepiadaceae	Bark	[73]
53.	Viscum calcaratum	Loranthaceae	Entire	[74]
54	Aphanamixis polystachya	Meliaceae	Stembark	[75]
55.	Pratia nummularia	Campanulaceae	Entire	[76]
56.	Aeonium arboretum	Crassulaceae	Leaf	[77]
57.	Ocotea foetens	Lauraceae	Branchlets	[77]
58.	Maytenus canariensis	Celastraceae	Fruit juice	[78]
59.	Sedum alboroseum	Crassulaceae	Entire	[79]
60.	Euphorbia micractina	Euphorbiacaeae	Entire	[80]
61.	Euphorbia prolifera	Euphorbiacaeae	Latex	[81]
62.	Scirpus holoschoenus	Cyperaceae	Inflorescence	[82]
63.	Dillenia suffruticosa	Dilleniaceae	Fruit	[83]
64	Hypoxis rooperii	Hypoxiaceae	Tuber	[84]
65.	Inula linariaefolia	Compositae	Flowers	[85]
66.	Ziziphus mauritiana	Rhamnaceae	Stem bark and Fruit	[86]
67.	Adiantum macrophyllum	Pteridaceae	Entire	[87]
68.	Thalictrum fabri	Ranunculaceae	Root	[88]
69.	Scutellaria indica	Labiatae	Root	[89]
70.	Hypericum japonicum	Guttiferae	Entire	[90]
71.	Cyathea fauriei	Cyatheaceae	Shoot	[91]
72.	Fissistigma oldhamii	Annonaceae	Stem	[92]
73.	Monnina obtusifolia	Polygalaceae	Aerial parts	[93]
74.	Coriolus versicolor	Polyporaceae	Fruitbody	[94]
75.	Melastoma malabathricum	Melatomataceae	Flower	[95]
76.	Carapa guianensis	Meliaceae	Seed oil	[96]
77.	Swietenia humilis	Meliaceae	Seed	[97]
78.	Ficus pretoiae	Moraceae	Sap	[98]

79.	Croton lechleri	Euphorbiacaeae	Latex	[99]
80.	Aster amellus	Compositae	Entire	[100]
81.	Crassocephalum bojeri	Compositae	Entire	[101]
82.	Echinops grijisii	Compositae	Root	[101]
83.	Adenium obesum	Apocynaceae	Leaf	[102]
84.	Ipomea batata	Convolvulaceae	Rhizome	[103]
85.	Uncaria tomentosa	Rubiaceae	Bark	[104]
86.	Plantago asiatica	Plantaginaceae	Leaf	[105]
87.	Phymatosorus diversifolium	Polydiaceae	Root	[105]
88.	Rabdosia rubescens	Labiatae	Leaf	[106]
89.	Salvia chinensis	Labiatae	Entire	[107]
90.	Ganoderma lucidum	Ganodermataceae	Fruitbody	[108]
91.	Euphorbia kansui	Euphorbiacaeae	Root	[109]
92.	Echinops latifolius	Compositae	Root	[110]
93.	Euphorbia marginata	Euphorbiacaeae	Entire	[111]
94.	Ligustrum lucidum	Oleaceae	Seed	[112]
95.	Phytolacca esculenta	Phytolaccaceae	Root	[113]
96.	Pinus parviflora	Pinaceae	Strobilus	[114]
97.	Dysosma pleiantha	Berberidaceae	Root	[115]
98.	Alnus japonica	Betulaceae	Wood	[116]
99.	Ruellia tuberose	Acanthaceae	Bark	[117]
100.	Acacia xanthophloea	Leguminosae	Fruit	[118]
101.	Lannea stuhlmannii	Anacardiaceae	Root	[118]
102.	Maytenus obscura	Celastraceae	Leaf	[118]
103.	Plicosepalus sagittifolius	Loranthaceae	Branches	[118]
104.	Piper latifolium	Piperaceae	Leaf	[119]
105.	Morinda citrifolia	Rubiaceae	Root	[119]
106.	Knema tenuinervia	Myristicaceae	Stembark	[120]
107.	Deeringia amaranthoides	Amaranthaceae	Fruit	[121]
108.	Cynanchum hancoekianum	Asclepiadaceae	Entire	[122]
109.	Azadirachta indica	Meliaceae	Leaf	[123]
110.	Virola bicuhyba	Myristicaceae	Seed	[124]
111.	Sempervivum armenum	Crassulaceae	Leaf	[125]
112.	Sempervivum arvense	Crassulaceae	Leaf	[125]
113.	Hippophae salicifolia	Elaeagnaceae	Fruit	[126]
114.	Hypoxis nyasica	Hypoxiaceae	Rhizome	[127]
115.	Astragalus membranaceus	Leguminosae	Root	[128]
116.	Maytenus macrocarpa	Celastraceae	Stembark	[129]
117.	Cephalotaxus Harrington	Cephlotaxaceae	Entire	[130]

Dietary source of anti cancer agents:

Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers. Recent studies suggest that the consumption of food rich in fruits, vegetables and spices have a lower incidence of cancers (stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas and colon) [131-133].

Dietary agents consist of a wide variety of biologically active components that are responsible for the anti-cancer effects like curcumin, genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, dithiolthiones, isothiocyanates, indole-3-carbinol, isoflavones, saponins, phytosterols, inositol hexaphosphate, Vitamin C, D-limonene, lutein, folic acid, beta carotene, selenium, Vitamin E and flavonoids (Table 3). Many of which have been used in traditional medicines for thousands of years. These dietary agents are believed to suppress the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis i.e angiogenesis and metastasis [134].

Table 3: Dietary sources as anticancer agent.

S. No.	Botanical Name	Source	Compound	Reference
1	Carica papaya, Family- Caricaceae	Berries	β-Cryptoxanthin	[135]
2	Glycyrrhiza glabra; Glycyrrhiza radix; Glycyrrhiza uralensis, Family- Leguminosae	Licorice root	Glycyrrhizin	[136]
3	Cannabis sativa, Family- Cannabiaceae	Hemp	Cannabinol	[137]
4	Rosmarinus officinalis, Family- Lamiaceae	Rosemary	Carnosol	[138]
5	Pueraria lobata radix, Family- Fabaceae		Genistein	[139]
6	Glycine max, Family- Fabaceae	Soybeans	Genistein	[139]
7	Prunus armeniaca, Family- Rosaceae	Apricots	Carotenoids	[140]
8	Zingiber officinale, Family- Zingiberaceae	Tuber	Gingerol	[141]
9	Lycopersicon esculentum, Family- Solanaceae	Tomato	Lycopene, Lutein, Kaempferol	[141]
10	Piper nigrum; Piper longum, Family- Piperaceae	Black pepper	Purpurogallin; Piperine	[142]
11	Ocimum sanctum, Family-Lamiaceae	Basil	Ursolic acid	[143]
12	Betula alba, Family- Betulaceae	Birch tree	Betulinic acid	[144]
13	Crocus sativus, Family- Iridaceae	Saffron	Carotenoids	[146]
14	Silymarin marianum, Family- Asteraceae	Milk thistle	Silymarin	[147]
15	Capsaicum annum; Capsaicum frutens, Family- Solanaceae	Red chilli	Capsaicinoids, Capsaicin	[148]
16	Camellia sinensis, Family- Theaceae	Green and black teas	Catechin and theaflavins	[149]
17	Vitis vinifera, Family- Vitaceae	Grapes	Resveratrol	[150]
18	Daucus carota sativus, Family- Apiaceae/umbelliferae	Carrot	β-Carotene	[151]
19	Tabebuia avellanedae, Family- Bignoniaceae	Lapacha tree	Lapachone	[31]
20	Citrus aurantium, Family- Rutaceae	Orange	Hesperidin	[152]
21	Prunus dulcis, Family- Rosaceae	Almond	Morin	[153,154]
22	Aloe arborescens, Family- Asphodelaceae	Aloe vera	Emodin	[155]
23	Opium poppy, Family- Paparveraceae	Poppy	Morphine and its analogues	[157]
24	Curcurbita moschata, Family-Cucurbitaceae	Pumpkin	β-Carotene	[158]
25	Azadirachata indica, Family- Meliaceae	Neem	Polyphenolics	[159]

Marines as source of anti-cancer agents:

Marine organisms are a rich source for natural products [160]. In recent time, advancement in deep-sea collection and aqua culture technology gives significant number of compounds derived from marine organisms entering preclinical and early clinical evaluation as potential anticancer agent [161,162]. Overall, more than 3000 new substances have been identified from marine organisms that demonstrate the great potential as a source of novel chemical classes [163]. Marine belongs to very diverse structural classes including polyketides, terpenes, steroids and peptides. The organisms yielding these bioactive marine compounds include invertebrate animals, algae, fungi and bacteria [164].

The first anticancer product didemnin B, a cyclic depsipeptide isolated from the tunicate Tridemnum solidum from marine source enter in clinical trials. Preliminary results showed a partial activity against non-Hodgkin's lymphoma [165]. It can inhibit protein synthesis and arrest G1 phase of cell-cycle. Another depsipeptide Aplidine appear to be more active as comparison with didemninB in preclinical trial and does not produce life-threatening neuromuscular toxicity. Preclinical data indicate that aplidine is active against several tumors through blockade of cell-cycle progression at G1 phase [166]. There are number of ecteinascidins have been isolated from the marine source tunicate Ecteinascidia turbinata. One of these ecteinascidins (ET-743) was selected for clinical trials and antitumor effects have been observed in phase I studies [167]. ET-743 is a tetrahydroisoquinilone alkaloid and they acts by selective alkylation of guanine residues in the DNA minor groove [168] and also interacts with nuclear proteins [169]. In Europe and the United States ET-743 is currently in phase II clinical trials [167]. The dolastatins are a class of peptides obtained from the Indian Ocean, Dolabella auricularia. These peptides have cytotoxic activity and now a day, dolastatin10 and dolastatin15 of this class have received the greatest clinical interest. Dolastatin10 has entered in Phase I and Phase II clinical trials, after showing significant antitumor activity in preclinical models [170]. Its mechanism of action involves inhibition of microtubule assembly ultimately result in cell-cycle arrest in metaphase [171,172]. The bryostatins, 20 macrocyclic lactones isolated from Bugula neritina and other marine bryozoa. These macrocyclic compounds have shown significant activity against lymphocytic leukemia cell line [173]. Bryostatin1 has recently entered phase II clinical trials for the treatment of melanoma, non-Hodgkin's lymphoma, renal cancer and colorectal cancer [174-176] and continues to be evaluated in phase I clinical trials. Bryostatin1 has been found to promote the normal growth of bone marrow progenitor cells, to provide in vivo protection against normally lethal doses of ionizing radiation and to serve as an immune stimulant, enhancing the normal production of interleukin2 and interferons [177].

Beside this there are the number of compounds isolated from marine as potential anti-cancer agents included in Table 4 [178,179].

Microorganisms as source of anti-cancer agents:

Antitumor antibiotics are among the most important cancer chemotherapeutic agents, and include members of the anthracycline, bleomycin, actinomycin, mitomycin and aureolic acid families [6]. Clinically useful agents from these above families are the daunomycin and related agents like doxorubicin, idarubicin and epirubicin; the peptolides (exemplified by dactinomycin), the mitosanes (such as mitomycin C) and the glycosylated anthracenone mithramycin. The anthracyclines are among the most used antitumor antibiotics in the clinic and exert antitumor activity mainly by inhibiting topoisomerase II [180,181].

Table 4: Marine derived potential anticancer agent.

S.No.	Compound	Organism	Chemistry	Mechanism of action
1.	Aaptamine	Sponge	Alkaloid	Induction of p21 and G2/M cell cycle arrest
2.	Cortistatin A	Sponge	Alkaloid	Selective inhibiton of angiogensis
3.	Aplidine	Ascidian	Depsipeptide	Oxidation and inactivation of low molecular weight-protein tyrosine phosphatase activity
4.	Bastadine 6	Sponge	Alkaloid	Inhibition of angiogenesis in vitro and in vivo involves apoptosis
5.	Fucoxanthinol	Ascidian	Carotenoid	Induction of apoptosis
6.	Lamellarin D	Mollusk	Alkaloid	ErbB3 protein and PI3K- Akt pathway involved in necrosis induction
7.	Clavulone II	Soft coral	Prostanoid	G1 cell cycle arrest and apoptosis
8.	Geodiamolides	Sponge	Peptide	Disorganization of actin filaments
9.	Ircinin-1	Sponge	Sesterterpene	G1 phase inhibition and apoptosis induction
10.	Laxaphycins A and B	Bacterium	Cyclic peptides	Increased polyploidy by putative topoisomerase II alterations
11.	Leptosins C and F	Fungus	Alkaloid	DNA topoisomerase I and II inhibition and apoptosis induction
12.	Onnamide A	Sponge	Polyketide	Protein synthesis inhibition
13.	Philinopside A	Sea cucumber	Saponin	Inhibition of angiogenesis and receptor tyrosine kinases
14.	Variolin B	Sponge	Alkaloid	Inhibition of cyclin-dependent kinases and apoptosis induction
15.	Aplidine	Ascidian	Depsipeptide	Induction of apoptosis with concomitant G1 arrest and G2 blockage
16.	Asciddemin	Ascidian	Alkaloid	Direct iminoquinone reduction and reactive oxygen species generation
17.	Cammbrescidin 800	Sponge	Alkaloid	Induction of eythroid differentiation and cell cycle arrest
18.	Dideoxypetrosynol A	Sponge	Fatty acid	Induction of apoptosis via mitochondrial signaling pathway
19.	Dolastatin 10	Mollusc	Peptide	Binds to amino-terminal peptide of β-tubulin containing cysteine
20.	Girolline	Sponge	Alkaloid	Induction of G2/M cell cycle arrest and p53 proteasome recruitment
21.	Halichondrin B analogues	Sponge	Macrolide derivative	Induction of mitotic blockage and apoptosis
22.	Lissoclinolide	Ascidian	Fatty acid	G2/M cell cycle arrest
23.	Neoamphimedine	Sponge	Alkaloid	Induction of topoisomerase II α-mediated catenation of DNA

24.	Psammaplin A	Sponge	Alkaloid	Inhibition of aminopeptidase N and suppression of angiogenesis in vitro
25.	Alkylpyridinium	Sponge	Alkaloid	Induction of apoptosis and reduced cell adhesion
26.	Aeroplysinin	Sponge	Alkaloid	Induction of apoptosis on proliferating endothelial cells
27.	Bryostatin-1	Bryozoan	Macrolide	Potentiation of ara-C induced apoptosis by PKC-dependent release of TNF-α
28.	Cephaiostatin	Worm	Steroid	Apoptosis and increased mitochondrial matrix density
29.	Chondropsin A	Sponge	Macrolide	In Vitro inhibition of V-ATPase enzyme
30.	Dehydrothrysiferol	Alga	Triterpene	Enhanced apoptosis induction in estrogen receptor negative breast cancer cells
31.	Diazonamide-A	Ascidian	Peptide	Disruption of mitosis and cellular microtubules with inhibition of GTP hydrolysis
32.	Dictyostatin	Sponge	Polyketide	Induction of tubulin polymerization
33.	Dolastatin 11	Mollusc	Peptide	F-actin stabilization by connection between two long-pitch strands
34.	Ecteinascidin- 743	Ascidian	Isoquinoline alkaloid	Telomere dysfunction increases susceptibility to ET-743
35.	GA3 polysaccharide	Alga	Polysaccharide	Inhibition of topoisomerase I and II
36.	Hemiasterlin analogue	Sponge	Tripeptide	Induction of microtubule depolymerisation
37.	Kahalalide F	Mollusc	Depsipeptide	Potent cytotoxicity and induction of necrosis
38.	Lamellarin D	Mollusc	Alkaloid	Potent inhibition of topoisomerase I
39.	omega-3 fatty acids	Fish	Fatty acid	--

Many pharmaceutical agents have been discovered by screening natural products from a wide range of microorganisms. Rapamycin and its analogs are products of Streptomyces hygroscopicus have potent immunosuppressive activity. They inhibit signaling pathways required for T-cell activation and proliferation. Rapamycin blocks progression of the cell cycle at middle-to-late G1 phase in T cells and B cells, and osteosarcoma and rhabdomyosarcoma cell lines, among others [182]. Geldanamycin is a benzoquinone ansamycin natural fermentation product and inhibits heat-shock protein HSP 90 [183].

Table 5: Microorganism derived anti-cancer agents.

S.No.	Compound	Microorganism	Used in Cancer
1.	Actinomycin	Streptomyces spp.	Sarcoma and germ-cell tumors
2.	Bleomycin	Streptomyces verticillus	Germ-cell, cervix and head and neck cancer
3.	Daunomycin	Streptomyces coeruleorubidus	Leukemia
4.	Doxorubicin	Streptomyces Pneuceticus	Lymphoma, breast, ovary, lung and sarcomas
5.	Epirubicin	Streptomyces pneuceticus	Breast cancer
6.	Idarubicin	Streptomyces Pneuceticus	Breast cancer and leukemia
7.	Mitomycin C	Streptomyces caespitosus	Gastric , colorectal, anal and lung cancer
8.	Geldanamycin	Streptomyces Hygroscopicus	Experimental
9.	Rapamicin	Streptomyces hygroscopicus	Experimental
10.	Wortamannin	Talaromyces wortmanni	Experimental

Wortmannin is a product of the fungus Talaromyces wortmanni and inhibits signal transduction pathways by forming a covalent complex with an active-site residue of phosphoinositide 3 kinase (PI3K), inhibiting PI3K activity [184] (Table 5). Thus, toxins that originally evolved to kill competing micoorganisms can have a variety of physiological effects in animals. In many cases, the targets of these compounds are components of signal transduction cascades that are conserved in many species, and that have been considered novel targets for anticancer drug discovery [185].

Conclusion:

Natural products have been a prime source for the treatment of many forms of cancer, many of which are consumed daily with the diet. They provide significant protection against various cancers and many other diseases. The antioxidant medicinal plants and their products prevent from the cancer and other diseases by protecting cells from damage. Thus, consuming a diet rich in antioxidant fruits, vegetables, herbs etc. will provide health-protective effects. Microbes and marine organisms also have been offering the great role in the prevention and treatment of cancer. All the natural products discussed in this review exhibit anticancer activities. Natural products offer a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

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