

## Review

# 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 (topotecan, irinotecan), 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 chlorophyll 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* (Cephalotaxaceae) [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  $\beta$ -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.   | <i>Salvia officinalis</i>                      | Labiatae        | Leaves                   | [32]       |
| 2.   | <i>Viscum album</i>                            | Loranthaceae    | Leaves                   | [33]       |
| 3.   | <i>Combretum caffrum</i>                       | Combretaceae    | Bark                     | [34]       |
| 4.   | <i>Melaleuca alternifolia</i>                  | Myrtaceae       | Leaves                   | [35]       |
| 5.   | <i>Lavandula angustifolia</i>                  | Labiatae        | Leaves                   | [35]       |
| 6.   | <i>Aglaia foveolata</i>                        | Meliaceae       | Fruit                    | [36]       |
| 7.   | <i>Maytenus serrata</i>                        | Celastraceae    | Seed                     | [37]       |
| 8.   | <i>Tabebuia impetiginosa</i>                   | Bignoniaceae    | Stem bark and trunk wood | [38,39]    |
| 9.   | <i>Tabebuia rosea</i>                          | Bignoniaceae    | Stem bark and trunk wood | [38,39]    |
| 10.  | <i>Tabebuia serratifolia</i>                   | Bignoniaceae    | Stem bark and trunk wood | [38,39]    |
| 11.  | <i>Dipteryx odorata</i>                        | Fabaceae        | Seed                     | [40]       |
| 12.  | <i>Thapsia garganica</i>                       | Apiaceae        | Fruit                    | [41]       |
| 13.  | <i>Indigofera tinctoria</i>                    | Leguminosae     | Aerial part              | [42]       |
| 14.  | <i>Matricaria chamomilla</i>                   | Asteraceae      | Flower                   | [43]       |
| 15.  | <i>Erythroxylum pervillei</i>                  | Erythroxylaceae | Root                     | [44]       |
| 16.  | <i>Broussonetia papyrifera</i>                 | Urticaceae      | Entire                   | [45]       |
| 17.  | <i>Cyclopia intermedia</i>                     | Fabaceae        | Leaves                   | [46]       |
| 18.  | <i>Scutellariae radix, Scutellariae indica</i> | Labiatae        | Root                     | [47]       |
| 19.  | <i>Physalis philadelphica</i>                  | Solanaceae      | Seed                     | [48]       |
| 20.  | <i>Dysoxylum binectariferum</i>                | Meliaceae       | Stem bark                | [49]       |
| 21.  | <i>Aristolochia chilensis</i>                  | Elaeocarpaceae  | Leaf and Stem            | [50]       |
| 22.  | <i>Cyathostemma argenteum</i>                  | Annonaceae      | Root                     | [51]       |
| 23.  | <i>Epimedium hunanense</i>                     | Berberidaceae   | Aerial parts             | [52]       |
| 24.  | <i>Croton urucurama</i>                        | Euphorbiaceae   | Bark                     | [53]       |
| 25.  | <i>Epilobium hirsutum</i>                      | Onagraceae      | Entire                   | [54]       |
| 26.  | <i>Pleione bulbocodioides</i>                  | Orchidaceae     | Tuber                    | [55]       |
| 27.  | <i>Cassia quinquangulata</i>                   | Caesalpiniaceae | Root                     | [56]       |
| 28.  | <i>Begonia glabra</i>                          | Begoniaceae     | Entire                   | [57]       |
| 29.  | <i>Celastrus orbiculatus</i>                   | Celastraceae    | Entire                   | [57]       |
| 30.  | <i>Croton draco</i>                            | Euphorbiaceae   | Aerial parts             | [57]       |
| 31.  | <i>Smilax sieboldii</i>                        | Liliaceae       | Entire                   | [58]       |
| 32.  | <i>Ximenia Americana</i>                       | Oleaceae        | 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          | Euphorbiaceae   | Leaf                | [65] |
| 40. | Euphorbia heterophylla  | Euphorbiaceae   | 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  | Euphorbiaceae   | 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    | Euphorbiaceae   | Entire              | [80] |
| 61. | Euphorbia prolifera     | Euphorbiaceae   | 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 | Melastomataceae | Flower              | [95] |
| 76. | Carapa guianensis       | Meliaceae       | Seed oil            | [96] |
| 77. | Swietenia humilis       | Meliaceae       | Seed                | [97] |
| 78. | Ficus pretoiiae         | Moraceae        | Sap                 | [98] |

|      |                                   |                 |           |       |
|------|-----------------------------------|-----------------|-----------|-------|
| 79.  | <i>Croton lechleri</i>            | Euphorbiaceae   | Latex     | [99]  |
| 80.  | <i>Aster amellus</i>              | Compositae      | Entire    | [100] |
| 81.  | <i>Crassocephalum bojeri</i>      | Compositae      | Entire    | [101] |
| 82.  | <i>Echinops grijsii</i>           | Compositae      | Root      | [101] |
| 83.  | <i>Adenium obesum</i>             | Apocynaceae     | Leaf      | [102] |
| 84.  | <i>Ipomea batata</i>              | Convolvulaceae  | Rhizome   | [103] |
| 85.  | <i>Uncaria tomentosa</i>          | Rubiaceae       | Bark      | [104] |
| 86.  | <i>Plantago asiatica</i>          | Plantaginaceae  | Leaf      | [105] |
| 87.  | <i>Phymatosorus diversifolium</i> | Polydiaceae     | Root      | [105] |
| 88.  | <i>Rabdosia rubescens</i>         | Labiatae        | Leaf      | [106] |
| 89.  | <i>Salvia chinensis</i>           | Labiatae        | Entire    | [107] |
| 90.  | <i>Ganoderma lucidum</i>          | Ganodermataceae | Fruitbody | [108] |
| 91.  | <i>Euphorbia kansui</i>           | Euphorbiaceae   | Root      | [109] |
| 92.  | <i>Echinops latifolius</i>        | Compositae      | Root      | [110] |
| 93.  | <i>Euphorbia marginata</i>        | Euphorbiaceae   | Entire    | [111] |
| 94.  | <i>Ligustrum lucidum</i>          | Oleaceae        | Seed      | [112] |
| 95.  | <i>Phytolacca esculenta</i>       | Phytolaccaceae  | Root      | [113] |
| 96.  | <i>Pinus parviflora</i>           | Pinaceae        | Strobilus | [114] |
| 97.  | <i>Dysosma pleiantha</i>          | Berberidaceae   | Root      | [115] |
| 98.  | <i>Alnus japonica</i>             | Betulaceae      | Wood      | [116] |
| 99.  | <i>Ruellia tuberosa</i>           | Acanthaceae     | Bark      | [117] |
| 100. | <i>Acacia xanthophloea</i>        | Leguminosae     | Fruit     | [118] |
| 101. | <i>Lanea stuhlmannii</i>          | Anacardiaceae   | Root      | [118] |
| 102. | <i>Maytenus obscura</i>           | Celastraceae    | Leaf      | [118] |
| 103. | <i>Plicosepalus sagittifolius</i> | Loranthaceae    | Branches  | [118] |
| 104. | <i>Piper latifolium</i>           | Piperaceae      | Leaf      | [119] |
| 105. | <i>Morinda citrifolia</i>         | Rubiaceae       | Root      | [119] |
| 106. | <i>Knema tenuinervia</i>          | Myristicaceae   | Stembark  | [120] |
| 107. | <i>Deeringia amaranthoides</i>    | Amaranthaceae   | Fruit     | [121] |
| 108. | <i>Cynanchum hancoekianum</i>     | Asclepiadaceae  | Entire    | [122] |
| 109. | <i>Azadirachta indica</i>         | Meliaceae       | Leaf      | [123] |
| 110. | <i>Viola bicuhyba</i>             | Myristicaceae   | Seed      | [124] |
| 111. | <i>Sempervivum armenum</i>        | Crassulaceae    | Leaf      | [125] |
| 112. | <i>Sempervivum arvense</i>        | Crassulaceae    | Leaf      | [125] |
| 113. | <i>Hippophae salicifolia</i>      | Elaeagnaceae    | Fruit     | [126] |
| 114. | <i>Hypoxis nyasica</i>            | Hypoxiaceae     | Rhizome   | [127] |
| 115. | <i>Astragalus membranaceus</i>    | Leguminosae     | Root      | [128] |
| 116. | <i>Maytenus macrocarpa</i>        | Celastraceae    | Stembark  | [129] |
| 117. | <i>Cephalotaxus Harrington</i>    | Cephalotaxaceae | 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      | <i>Carica papaya</i> , Family- Caricaceae                                                                 | Berries              | $\beta$ -Cryptoxanthin       | [135]     |
| 2      | <i>Glycyrrhiza glabra</i> ; <i>Glycyrrhiza radix</i> ; <i>Glycyrrhiza uralensis</i> , Family- Leguminosae | Licorice root        | Glycyrrhizin                 | [136]     |
| 3      | <i>Cannabis sativa</i> , Family- Cannabiaceae                                                             | Hemp                 | Cannabinol                   | [137]     |
| 4      | <i>Rosmarinus officinalis</i> , Family- Lamiaceae                                                         | Rosemary             | Carnosol                     | [138]     |
| 5      | <i>Pueraria lobata radix</i> , Family- Fabaceae                                                           |                      | Genistein                    | [139]     |
| 6      | <i>Glycine max</i> , Family- Fabaceae                                                                     | Soybeans             | Genistein                    | [139]     |
| 7      | <i>Prunus armeniaca</i> , Family- Rosaceae                                                                | Apricots             | Carotenoids                  | [140]     |
| 8      | <i>Zingiber officinale</i> , Family- Zingiberaceae                                                        | Tuber                | Gingerol                     | [141]     |
| 9      | <i>Lycopersicon esculentum</i> , Family- Solanaceae                                                       | Tomato               | Lycopene, Lutein, Kaempferol | [141]     |
| 10     | <i>Piper nigrum</i> ; <i>Piper longum</i> , Family- Piperaceae                                            | Black pepper         | Purpurogallin; Piperine      | [142]     |
| 11     | <i>Ocimum sanctum</i> , Family-Lamiaceae                                                                  | Basil                | Ursolic acid                 | [143]     |
| 12     | <i>Betula alba</i> , Family- Betulaceae                                                                   | Birch tree           | Betulinic acid               | [144]     |
| 13     | <i>Crocus sativus</i> , Family- Iridaceae                                                                 | Saffron              | Carotenoids                  | [146]     |
| 14     | <i>Silymarin marianum</i> , Family- Asteraceae                                                            | Milk thistle         | Silymarin                    | [147]     |
| 15     | <i>Capsaicum annum</i> ; <i>Capsaicum frutens</i> , Family- Solanaceae                                    | Red chilli           | Capsaicinoids, Capsaicin     | [148]     |
| 16     | <i>Camellia sinensis</i> , Family- Theaceae                                                               | Green and black teas | Catechin and theaflavins     | [149]     |
| 17     | <i>Vitis vinifera</i> , Family- Vitaceae                                                                  | Grapes               | Resveratrol                  | [150]     |
| 18     | <i>Daucus carota sativus</i> , Family- Apiaceae/umbelliferae                                              | Carrot               | $\beta$ -Carotene            | [151]     |
| 19     | <i>Tabebuia avellanedae</i> , Family- Bignoniaceae                                                        | Lapacha tree         | Lapachone                    | [31]      |
| 20     | <i>Citrus aurantium</i> , Family- Rutaceae                                                                | Orange               | Hesperidin                   | [152]     |
| 21     | <i>Prunus dulcis</i> , Family- Rosaceae                                                                   | Almond               | Morin                        | [153,154] |
| 22     | <i>Aloe arborescens</i> , Family- Asphodelaceae                                                           | Aloe vera            | Emodin                       | [155]     |
| 23     | Opium poppy, Family- Paparveraceae                                                                        | Poppy                | Morphine and its analogues   | [157]     |
| 24     | <i>Curcubita moschata</i> , Family-Cucurbitaceae                                                          | Pumpkin              | $\beta$ -Carotene            | [158]     |
| 25     | <i>Azadirachata indica</i> , 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 *Trididemnum 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.**

| <b>S.No.</b> | <b>Compound</b>          | <b>Organism</b> | <b>Chemistry</b>     | <b>Mechanism of action</b>                                                               |
|--------------|--------------------------|-----------------|----------------------|------------------------------------------------------------------------------------------|
| 1.           | Aaptamine                | Sponge          | Alkaloid             | Induction of p21 and G2/M cell cycle arrest                                              |
| 2.           | Cortistatin A            | Sponge          | Alkaloid             | Selective inhibition of angiogenesis                                                     |
| 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.          | Ascididemin              | Ascidian        | Alkaloid             | Direct iminoquinone reduction and reactive oxygen species generation                     |
| 17.          | Cammbrescidin 800        | Sponge          | Alkaloid             | Induction of erythroid 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 $\beta$ -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 $\alpha$ -mediated catenation of DNA                       |



|     |                       |          |                       |                                                                                   |
|-----|-----------------------|----------|-----------------------|-----------------------------------------------------------------------------------|
| 24. | Psammaphin 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. | Aeropylsinin          | Sponge   | Alkaloid              | Induction of apoptosis on proliferating endothelial cells                         |
| 27. | Bryostatin-1          | Bryozoan | Macrolide             | Potential of ara-C induced apoptosis by PKC-dependent release of TNF- $\alpha$    |
| 28. | Cephaiostatin         | Worm     | Steroid               | Apoptosis and increased mitochondrial matrix density                              |
| 29. | Chondropsin A         | Sponge   | Macrolide             | In Vitro inhibition of V-ATPase enzyme                                            |
| 30. | Dehydrothysiferol     | 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. | Ecteinasidin- 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.    | Rapamycin    | Streptomyces hygroscopicus   | Experimental                               |
| 10.   | Wortmannin   | 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 microorganisms 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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