Review Article

NATURAL REMEDIES WITH POTENTIAL ANTI-CANCER ACTIVITY AND ROLE OF PLANT TISSUE CULTURE IN DEVELOPMENT OF THOSE REMEDIES: A REVIEW

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ABSTRACT

At present times, Herbal remedies occupy an important position for being the paramount sources of drug discovery, irrespective of its categorized groups in which including herbs, Shrubs or trees. Plants have been indispensable in treating diverse form of diseases including cancer. Cancer is not just one disease but many diseases. There are more than 100 different types of cancer 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) and tissue culture are the most important technique for the development of those remedies in short duration of time tissue culture are also useful to produce many copies in any time of the same plants then which may be used to produce plants with better flowers, odour's, fruits or any other properties of the plants that is beneficial to the human beings

Keywords: Cancer, Herbal remedies, Dietary remedies, Marine remedies, Micro-organism

INTRODUCTION

Cancer is a dreadful disease characterized by the irregular proliferation of the cells. As a cell progresses from normal to cancerous, the biological imperative to survive and perpetuate drives fundamental changes in cells behaviour. So the actual cause of the disease in different sections is still to be explored clearly. Cancer is thus, a class of disease, classified by the type of cell that is initially affected. Today's global scenario indicates that breast cancer and colorectal cancer is the most prominent cancer in case of women and men. To combat cancer United States national cancer institute has undergone 2069 anticancer clinical trials, in which over 150 drug combination have been successfully recorded against cancer. There is no one definition that describes all

cancers. They are a large family of diseases which form a subset of neoplasms, which show some features that suggest of malignancy. A neoplasm or tumour is a group of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely.^{3,4} Six characteristics of malignancies have been proposed: sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis and activating invasion and metastasis. The progression from normal cells to cells that can form a discernible mass to outright cancer involves multiple steps.^{7,8}

Sign and Symptoms of cancer

Fever

Fever is very common with cancer, but it more often happens after cancer has spread from where it started, fast breathing, and abnormal lung sounds heard through a stethoscope.

Weight loss

Unexplained weight loss, this happens most often with cancers of the pancreas, stomach, oesophagus (swallowing tube), or lung.

Fatigue

Fatigue may happen early, though, in some cancers, like leukemia. Some colon or stomach cancers can cause blood loss that's not obvious. This is another way cancer can cause fatigue.

Pain

Pain may be an early symptom with some cancers like bone cancers or testicular cancer. Back pain can be a symptom of cancer of the colon, rectum, or ovary. Most often, pain due to cancer means it has already spread (metastasized) from where it started.

Causes of cancer

Cancers are primarily an environmental disease with 90–95 % of cases attributed to environmental factors and 5–10 % due to genetics. Environmental, as used by cancer researchers, means any cause that is not inherited genetically, not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30 %), diet and obesity (30–35 %), infections (15–20 %), radiation (both ionizing and non-ionizing, up to 10 %), stress, lack of physical activity, and environmental pollutants. It is nearly impossible to prove what caused a cancer in any individual, because most cancers have multiple possible causes. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, then there is a small chance that the cancer developed because of air pollution or radiation.^{10,11}

Skin changes

Along with cancers of the skin, some other cancers can cause skin changes that can be seen. These signs and symptoms include:

- Darker looking skin (hyper pigmentation)
- Yellowish skin and eyes (jaundice)
- Reddened skin (erythema)
- Itching (pruritis)
- Excessive hair growth

Long-term constipation

Diarrhoea or a change in the size of the stool may be a sign of colon cancer. Pain when passing urine, blood in the urine, or a change in bladder function (such as needing to pass urine more or less often than usual) could be related to bladder or prostate cancer. Skin cancers may bleed and look like sores that don't heal.

Sore

A long-lasting sore in the mouth could be an oral cancer. This should be dealt with right away, especially in people who smoke, chew tobacco, or often drink alcohol. Sores on the penis or vagina may either be signs of infection or an early cancer, and should be seen by a health professional.

White patches/white spot

White patches inside the mouth and white spots on the tongue may be leukoplakia. Leukoplakia is a pre-cancerous area that's caused by frequent irritation. It's often caused by smoking or other tobacco use. People who smoke pipes or

Types of cancer

Cancer is not just one disease but many diseases. There are more than 100 different types of cancer. Most cancers are

Cancer types can be grouped into broader categories. The main categories of cancer include:

Carcinoma

Cancer that begins in the skin or in tissues that line or cover internal organs; there are a number of subtypes of carcinoma, including adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.

Sarcoma

Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue

Leukemia

Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood

Lymphoma and myeloma

Cancers that begin in the cells of the immune system

Central nervous system cancers

Cancers that begin in the tissues of the brain and spinal cord

Germ cell tumour

Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

use oral or spit tobacco are at high risk for leukoplakia. If it's not treated, leukoplakia can become mouth cancer. Any long-lasting mouth changes should be checked by a doctor or dentist right away.

Coughing and unusual bleeding

Unusual bleeding can happen in early or advanced cancer. Coughing up blood in the sputum (phlegm) may be a sign of lung cancer. Blood in the stool (which can look like very dark or black stool) could be a sign of colon or rectal cancer. Cancer of the cervix or the endometrium (lining of the uterus) can cause abnormal vaginal bleeding. Blood in the urine may be a sign of bladder or kidney cancer. A bloody discharge from the nipple may be a sign of breast cancer.

Lumps and nodes

A lump or thickening in breast, lymph nodes and testis may be an early or late sign of cancer, especially if it has grown in size. Some breast cancers show up as red or thickened skin rather than the expected lump.

Indigestion or swallowing

Indigestion or swallowing problems that don't go away may be signs of cancer of the oesophagus (the swallowing tube that goes to the stomach), stomach, or pharynx (throat). But like most symptoms on this list, they are most often caused by something other than cancer. A cough that does not go away may be a sign of lung cancer. Hoarseness can be a sign of cancer of the voice box (larynx) or thyroid gland.²

named for the organ or type of cell in which they start - for example, cancer that begins in the colon is called colon cancer; cancer that begins in melanocytes of the skin is called melanoma.

Blastoma

Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults.⁹

Stages of cancer

Overall Stage Grouping is also referred to as Roman Numeral Staging. This system uses numerals I, II, III, and IV (plus the 0) to describe the progression of cancer.

Stage 0: carcinoma in situ.

Stage I: cancers are localized to one part of the body. Stage I cancer can be surgically removed if small enough.

Stage II: cancers are locally advanced. Stage II cancer can be treated by chemo, radiation, or surgery.

Stage III: cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III can depend on the specific type of cancer; for example, in Hodgkin's disease, Stage II indicates affected lymph nodes on only one side of the diaphragm, whereas Stage III indicates affected lymph nodes above and below the diaphragm. The specific criteria for Stages II and III therefore differ according to diagnosis. Stage III can be treated by chemo, radiation, or surgery

Stage IV: cancers have often metastasized, or spread to other organs or throughout the body. Stage IV cancer can be treated by chemo, radiation, or surgery.^{5,6}

Prevention of cancer

In 2008 approximately 12.7 million cancers were diagnosed (excluding non-melanoma skin cancers and other non-invasive cancers) and in 2010 nearly 7.98 million people died. Cancers as a group account for approximately 13 % of all deaths each year with the most common being: lung cancer (1.4 million deaths), stomach cancer (740,000 deaths), liver cancer (700,000 deaths), colorectal cancer (610,000 deaths), and breast cancer (460,000 deaths). This makes invasive cancer the leading cause of death in the developed world and the second leading cause of death in the developing world. Over half of cases occur in the developing world. Because cancer is a class of diseases, it is unlikely that there will ever be a single "cure for cancer" any more than there will be a single treatment for all infectious diseases. Angiogenesis inhibitors were once thought to have potential as a "silver bullet" treatment applicable to many types of cancer, but this has not been the case in practice. Experimental cancer treatments are treatments that are being studied to see whether they work. Typically, these are studied in clinical trials to compare the proposed treatment to the best existing treatment. They may be entirely new treatments, or they may be treatments that have been used successfully in one type of cancer, and are now being tested to see whether they are effective in another type. More and more, such treatments are being developed alongside companion diagnostic tests to target the right drugs to the right patients, based on their individual biology. Cancer research is the intense scientific effort to understand disease processes and discover possible therapies. Research about cancer causes focuses on the following issues:

- Agents (e.g. viruses) and events (e.g. mutations) which cause or facilitate genetic changes in cells destined to become cancer.
- The precise nature of the genetic damage, and the genes which are affected by it.
- The consequences of those genetic changes on the biology of the cell, both in generating the defining properties of a cancer cell, and in facilitating additional genetic events which lead to further progression of the cancer. The improved understanding of molecular biology and cellular biology due to cancer research has led to a number of new treatments for cancer since U.S. President Nixon declared the "War on Cancer" in 1971. Since then, the U.S. has spent over \$200 billion on cancer research, including resources from the public and private sectors and foundations during that time, the country has seen a five percent decrease in the cancer death rate (adjusting for size and age of the population) between 1950 and 2005.¹⁸⁷

Herbal Remedies with Potential Anti-cancer Activity

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 leukemia¹². Vincristine inhibits microtubule assembly, inducing tubulin self-association into coiled spiral aggregates¹³. Etoposide is an epipodophyllotoxin, derived from the mandrake plant *Podophyllum peltatum* and the wild chervil *Podophyllum emodi*¹⁴. It has also significant activity against small-cell lung carcinoma¹⁵. Etoposide is a topoisomerase II inhibitor, stabilizing enzyme-DNA cleavable complexes leading to DNA breaks¹⁶. 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 arrest¹⁷. 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 *Nyssaceae camptotheca acuminate* and act by inhibiting topoisomerase I²⁰. The taxanes and the camptothecins are presently approved for human use in various countries 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 trial²³. 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 progression²⁷. It has shown efficacy against various leukemias²⁸. A lung-cancer-specific anti neoplastic 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 lung³⁰. 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 breast³¹. 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 1)

Table 1: Herbal remedies 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 cafrum</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</i> , <i>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.	<i>Maytenus emarginata</i>	Celastraceae	Entire	[59]
34.	<i>Sarcandra glabra</i>	Choranthaceae	Entire	[60]
35.	<i>Salvia plebeian</i>	Labiatae	Aerial	[61]
36.	<i>Scutellaria barbata</i>	Labiatae	Entire	[62]
37.	<i>Ocotea caparrapi</i>	Lauraceae	Essential oil	[63]
38.	<i>Caragana cuneata</i>	Leguminosae	Leaf	[64]
39.	<i>Croton flavens</i>	Euphorbiaceae	Leaf	[65]
40.	<i>Euphorbia heterophylla</i>	Euphorbiaceae	Stem	[65]
41.	<i>Echites vucatanensis</i>	Apocynaceae	Latex	[65]
42.	<i>Thevetia ahouia</i>	Apocynaceae	Leaf and Stem	[65]
43.	<i>Thevetia gaumeri</i>	Apocynaceae	Leaf and Stem	[65]
44.	<i>Thevetia peruviana</i>	Apocynaceae	Leaf and Stem	[65]
45.	<i>Euphorbia ebracteolata</i>	Euphorbiaceae	Aerial parts	[66]
46.	<i>Dioscorea collettii</i>	Dioscoreaceae	Rhizome	[67]
47.	<i>Juglans mandshurica</i>	Juglandaceae	Root	[68]
48.	<i>Maackia tenuifolia</i>	Leguminosae	Root	[69]
49.	<i>Juncus acutus</i>	Juncaceae	Leaf	[70]
50.	<i>Hedyotis chrysotricha</i>	Rubiaceae	Entire	[71]
51.	<i>Arisaema erubescens</i>	Araceae	Root	[72]
52.	<i>Leptadenia hastata</i>	Asclepiadaceae	Bark	[73]
53.	<i>Viscum calcaratum</i>	Loranthaceae	Entire	[74]
54.	<i>Aphanamixis polystachya</i>	Meliaceae	Stembark	[75]
55.	<i>Pratia nummularia</i>	Campanulaceae	Entire	[76]
56.	<i>Aeonium arboreum</i>	Crassulaceae	Leaf	[77]
57.	<i>Ocotea foetens</i>	Lauraceae	Branchlets	[77]
58.	<i>Maytenus canariensis</i>	Celastraceae	Fruit juice	[78]
59.	<i>Sedum alboroseum</i>	Crassulaceae	Entire	[79]
60.	<i>Euphorbia micractina</i>	Euphorbiaceae	Entire	[80]
61.	<i>Euphorbia prolifera</i>	Euphorbiaceae	Latex	[81]
62.	<i>Scirpus holoschoenus</i>	Cyperaceae	Inflorescence	[82]
63.	<i>Dillenia suffruticosa</i>	Dilleniaceae	Fruit	[83]
64.	<i>Hypoxis rooperii</i>	Hypoxiaceae	Tuber	[84]
65.	<i>Inula linariaefolia</i>	Compositae	Flowers	[85]
66.	<i>Ziziphus mauritiana</i>	Rhamnaceae	Stem bark and Fruit	[86]
67.	<i>Adiantum macrophyllum</i>	Pteridaceae	Entire	[87]
68.	<i>Thalictrum fabri</i>	Ranunculaceae	Root	[88]
69.	<i>Scutellaria indica</i>	Labiatae	Root	[89]
70.	<i>Hypericum japonicum</i>	Guttiferae	Entire	[90]
71.	<i>Cyathea fauriei</i>	Cyatheaceae	Shoot	[91]
72.	<i>Fissistigma oldhamii</i>	Annonaceae	Stem	[92]

73.	<i>Monnina obtusifolia</i>	Polygalaceae	Aerial parts	[93]
74.	<i>Coriolus versicolor</i>	Polyporaceae	Fruitbody	[94]
75.	<i>Melastoma malabathricum</i>	Melastomataceae	Flower	[95]
76.	<i>Carapa guianensis</i>	Meliaceae	Seed oil	[96]
77.	<i>Swietenia humilis</i>	Meliaceae	Seed	[97]
78.	<i>Ficus pretoiiae</i>	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 grijisii</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>Lannea 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 biculhyba</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]

Natural Dietary Remedies 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, oesophagus, 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. 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, hyper proliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis i.e. angiogenesis and metastasis (Table 2)¹³⁴.

Table 2: Dietary sources as anticancer agent¹⁸⁶

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

Marine Remedies as Source of Anti-cancer Agents¹⁶⁰

Marine organisms are a rich source for natural products¹⁶⁰. 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 classes¹⁶³. 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 bacteria¹⁶⁴. 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 lymphoma¹⁶⁵. It can inhibit protein synthesis and arrest G1 phase of cell-cycle. Another depsipeptide Aplidine appear to be more active as comparison with didemnin B in preclinical trial and does not produce life-threatening neuromuscular toxicity. Preclinical data indicate that aplidine is active against several tumours through blockade of cell-cycle progression at G1 phase¹⁶⁶. 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 studies¹⁶⁷. ET-743 is a

tetrahydroisoquinilone alkaloid and they acts by selective alkylation of guanine residues in the DNA minor groove¹⁶⁸ and also interacts with nuclear proteins¹⁶⁹. In Europe and the United States ET-743 is currently in phase II clinical trials¹⁶⁷. The dolastatins are a class of peptides obtained from the Indian Ocean, *Dolabella auricularia*. These peptides have cytotoxic activity and now a day, dolastatin 10 and dolastatin 15 of this class have received the greatest clinical interest. Dolastatin 10 has entered in Phase I and Phase II clinical trials, after showing significant antitumor activity in preclinical models¹⁷⁰. Its mechanism of action involves inhibition of microtubule assembly ultimately result in cell-cycle arrest in metaphase^{171,172}. The bryostatins, 20 macro cyclic lactones isolated from *Bugula neritina* and other marine bryozoa. These macro cyclic compounds have shown significant activity against lymphocytic leukemia cell line¹⁷³. Bryostatin1 has recently entered phase II clinical trials for the treatment of melanoma, non-Hodgkin's lymphoma, renal cancer and colorectal cancer¹⁷⁴⁻¹⁷⁶ 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 interferons¹⁷⁷. Beside this there is the number of compounds isolated from marine as potential anti-cancer agents included in Table 3^{178,179}

Table 3: Marine derived potential anticancer agent¹⁸⁶

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 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.	Ascidimemin	Ascidian	Alkaloid	Direct iminoquinone reduction and reactive oxygen species generation
17.	Cammbrescidin 800	Sponge	Alkaloid	Induction of cythroid 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.	Giroline	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.	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.	Aeroplysin	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- α
28.	Cephaiostatin	Worm	Steroid	Apoptosis and increased mitochondrial matrix density
29.	Chondropsin A	Sponge	Macrolide	In Vitro inhibition of V-ATPase enzyme
30.	Dehydrothrysisferol	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.	Hemiassterlin 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	--

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 families⁶. 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}. 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 activity¹⁸⁴. Thus, toxins that originally evolved to kill competing micro organisms 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 (Table 4)¹⁸⁵.

Table 4: Microorganism derived anti-cancer agents¹⁸⁶

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

Role of Plant Tissue Culture in Development of Anti-cancer Remedies

- To produce many copies of the same plants then which may be used to produce plants with better flowers, odours, fruits or any other properties of the plants that is beneficial to the human beings.
- To produce plants anytime we want although the climates are not appropriate to produce a plant. Moreover, if seed is not available, it is possible to produce a plant with this method.
- If there is plant with partially infected tissue, it is possible to produce a new plant without infection.
- Very helpful in the genetically modified organism studies.
- Very useful solution for the prevention of starvation in third world countries since the process is highly efficient, by using only one plant, it is possible to produce more than one thousand of the same plant with higher productive if its genome changed.
- The biochemical engineer can grow plant cells in liquid culture on a large scale—Bioreactor
- The production of diploid plants from haploid cultures shortens the time taken to achieve uniform homozygous lines and varieties.
- The crossing of distantly related species by protoplast isolation and somatic fusion increases the possibility for the transfer and expression of novel variation in domestic crops.
- Cell selection increases the potential number of individuals in a screening program.
- Micro propagation using meristem and shoot culture techniques allows the production of large numbers of uniform individuals of species from limited starting material.
- Genetic transformation of cells enables very specific information to be introduced into single cells which can then be regenerated¹⁸⁷

CONCLUSION

According to World Health Organisation, 80 % of people living in the rural areas depend on medicinal plants as primary health care system. These practices are solely based on the knowledge of traditional use of herbal remedies, natural dietary remedies, marine remedies and micro-organism as a source of medicine. These products are formulated to generate different types of effective drugs to enhance anti-cancer activities. Plant tissue culture is most important and easy way to increase the quality and quantity of that remedies which are useful for the cure of cancer in short time of period. This review revealed that many of medicinal plants used by traditional healer are reported to have scientific evidence. 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 and tissue culture, increases the amount of planting material to facilitate distribution and large scale planting. In this way, thousands of copies of a plant can be produced in a short time. Micro propagated plants are observed to establish more quickly, grow more vigorously and are taller, have a shorter and more uniform production cycle, and produce higher yields than conventional propagules.

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