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NATUREVOLUTION EFFECTIVE AGAINST CANCER THERAPY– REVIEW (TREATING CANCER DISEASES USING PLANT PRODUCTS)

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ABSTRACT

Naturevolution is a term necessary to evaluate ourselves in term metabolism of natural metabolites. Our studies insist on natural products more extremely powerful treatment for cancer cures. The truth is they actually hate people using any form of natural cures for cancer. Mainly anticancer agents are obtained from plants (vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan and irinotecan), marine organisms (citarabine, aplidine and dolastatin 10) and micro-organisms (dactinomycin, bleomycin and doxorubicin)some of the fruits and vegetables also has anticancer activity.some of the plant products which are in daily usage are capsaicin (red chilli), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallyl sulfide (allium), S-allyl cysteine (allium), allicin (garlic), lycopene (tomato), 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 the active principle obtained from natural products and novel lead compounds along with mechanism of action has been included.

KEYWORDS: Cancer, naturevolution, natural resource,fruits and vegetables.

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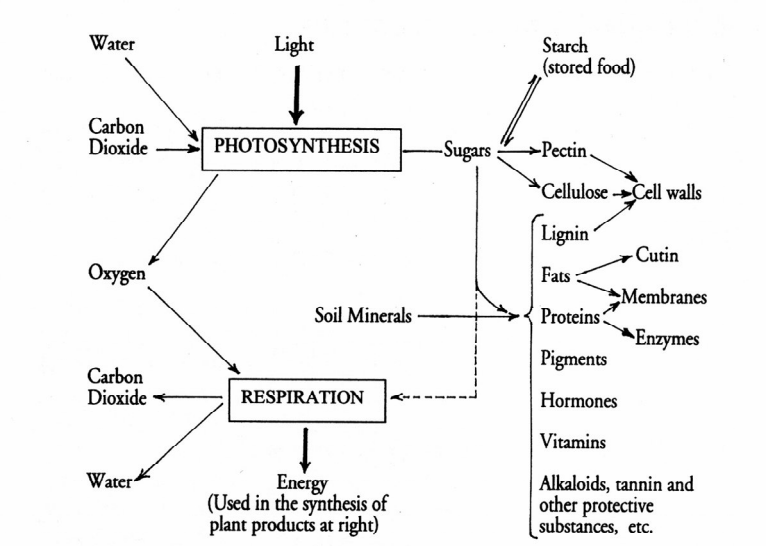
INTRODUCTION

Metabolites are the intermediates and products of metabolism.generally the metabolites are small molecules. Metabolites have various functions, including fuel, structure, signalling, stimulatory and inhibitory effects on enzymes, catalytic activity of their own (usually as a cofactor to an enzyme), defense, and interactions with other organisms (e.g. pigments, odorants, and pheromones).primary metabolites are involved in normal growt,development and reproduction.alcohol belongs to primary metabolite.secondary metabolites are involved in ecological function.Antibiotics and pigments include resins and terpenes belongs to secondary metabolites.Antibiotics like actinomycin uses primary metabolites as precursors. A primary metabolite is also known as central metabolite mainly present in many microorganisms and cells. Conversely, a secondary metabolite is not directly involved in those processes, but usually has an important ecological function (i.e. a relational function). A secondary metabolite is typically present in a taxonomically restricted set of organisms or cells (Plants, Fungi, Bacteria...) Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of an organism[1]. Unlike primary metabolites, absence of secondary metabolites does not result in immediate death, but rather in long-term impairment of the organism's survivability, fecundity, or aesthetics, or perhaps in no significant change at all. Secondary metabolites are often restricted to a narrow set of species within a phylogenetic group[2]. Secondary metabolites often play an important role in plant defense against herbivory and other interspecies defenses.Humans are using secondary metabolites as drugs,flavourings and recreational drugs.



An outline of plant metabolism

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 the 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 came 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]. 23 new drugs obtained from natural products were introduced in between 2001 to 2005 for treating various disorders like bacterial,fungal infections,cancer,diabetes and for some genetic disorders,out of 23 drugs only 4 drugs has anticancer activity. 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.

Oxidation is a chemical resction involves transfer of electrons or hydrogen from a substance to oxidising agent.Oxidation reaction produce free radicals,these radicals are involved in chain reactions.If chain reactions occur in cells leads to damage or death.Generally antioxidants are used for prevention of oxidation reaction.they shows the action by terminating chain reactions.So antioxidants are reducing agents such as thiols,ascorbic acid,polyphenols are used for inhibiting gum formation in petrol.plants and animals contain several types of antioxidants such as vitamin A,C,E and some enzymes like catalase,various peroxidises.If antioxidant levels are decreased leads to damage of cells or some times cause death of cells.Oxidative stress seems to play a significant role in many human diseases, including cancers.For treatment of stroke and neurodegenerative diseases antioxidants are extensively used. For these reasons, oxidative stress can be considered to be both the cause and the consequence of some diseases. Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer, coronary heart disease and even altitude sickness

Plants as source of anti-cancer agents

Plants that indicate potential as an anticancer agent in laboratory-based *in vitro* research – for example, are currently being studied. There can be many years between promising laboratory work and the availability of an effective anti-cancer drug. Monroe Eliot Wall discovered anti-cancer properties in *Camptotheca* in 1958, but it was not until 1996 – after further research and rounds of clinical trials – that a derived drug was approved for use by the US Food and Drug Administration.[7] Herbal medicine takes a whole-body approach to promoting health, in which the physical remedy is but one part of the treatment. Although herbalists use substances made from plants, they don't extract them in the same intense way as the drug industry; they believe that their remedies are effective because of the delicate chemistry of the plant as a whole.[8] 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]. Vinca alkaloids are a set of anti-mitotic and anti-

microtubule agents that were originally derived from the Periwinkle plant *Catharanthus roseus*.Vinca alkaloids are used in the treatment of cancer. They are a class of cell-cycle-specific cytotoxic drugs that work by inhibiting the ability of cancer cells to divide: Acting upon tubulin, they prevent it from forming into microtubules, a necessary component for cellular division. Vinca alkaloids are now produced synthetically and used as drugs in cancer therapy and as immunosuppressive drugs. These compounds include vinblastine, vincristine, vindesine, and vinorelbine.

Etoposide is an epipodophyllotoxin, derived from the mandrake plant Podophyllum peltatum and the wild chervil Podophyllum emodi[14]. It also has 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 clinical 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). 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].

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

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[33]

S.No.	Plant Species	Family	Plant Part
1.	Salvia officinalis	Labiatae	Leaves
2.	Viscum album	Loranthaceae	Leaves
3.	Melaleuca alternifolia	Myrtaceae	Leaves
4.	Lavandula angustifolia	Labiatae	Leaves
5.	Cyclopia intermedia	Fabaceae	Leaves
6.	Juncus acutus	Juncaceae	Leaf
7.	Aeonium arboretum	Crassulaceae	Leaf
8.	Piper latifolium	Piperaceae	Leaf
9.	Maytenus obscura	Celastraceae	Leaf
10.	Caragana cuneata	Leguminosae	Leaf
11.	Croton flavens	Euphorbiacaeae	Leaf
12.	Plantago asiatica	Plantaginaceae	Leaf
13.	Rabdosia rubescens	Labiatae	Leaf
14.	Adenium obesum	Apocynaceae	Leaf
15.	Azadirachta indica	Meliaceae	Leaf
16.	Sempervivum armenum	Crassulaceae	Leaf
17.	Sempervivum arvense	Crassulaceae	Leaf
18.	Thevetia gaumeri	Apocynaceae	Leaf and Stem
19.	Thevetia peruciana	Apocynaceae	Leaf and Stem
20.	Indigofera tinctoria	Leguminosae	Aerial part
21.	Epimedium hunanense	Berberidaceae	Aerial parts
22.	Physalis philadelphica	Solanaceae	Seed
23.	Croton urucurama	Euphorbiacaeae	Bark
24.	Combretum caffrum	Combretaceae	Bark
25.	Leptadenia hastate	Asclepiadaceae	Bark
26.	Pleione bulbocodioides	Orchidaceae	Tuber
27.	Broussonetia papyrifera	Urticaceae	Entire
28.	Epilobium hirsutum	Onagraceae	Entire
29.	Smilax sieboldii	Liliaceae	Entire
30.	Maytenus emarginata	Celastraceae	Entire
31.	Sarcandra glabra	Choranthaceae	Entire
32.	Adiantum macrophyllum	Pteridaceae	Entire
33.	Euphorbia micractina	Euphorbiacaeae	Entire
34.	Sedum alboroseum	Crassulaceae	Entire
35.	Cephalotaxus Harrington	Cephlotaxaceae	Entire
36.	Viscum calcaratum	Loranthaceae	Entire
37.	Scutellaria barbata	Labiatae	Entire
38.	Salvia chinensis	Labiatae	Entire
39.	Euphorbia marginata	Euphorbiacaeae	Entire
40.	Aster amellus	Compositae	Entire
41.	Crassocephalum bojeri	Compositae	Entire
42.	Pratia nummularia	Campanulaceae	Entire
43.	Hypericum japonicum	Guttiferae	Entire
44.	Cynanchum hancoekianum	Asclepiadaceae	Entire
45.	Erythroxylum pervillei	Erythroxylaceae	Root
46.	Ximenia Americana	Olacaceae	Root
47.	Scutellariae radix, Scutellariae indica	Labiatae	Root
48.	Juglans mandshurica	Juglandaceae	Root
49.	Maackia tenuifolia	Leguminosae	Root
50.	Arisaema erubescens	Araceae	Root
51.	Echinops grijisii	Compositae	Root
52.	Euphorbia kansui	Euphorbiacaeae	Root
53.	Echinops latifolius	Compositae	Root
54.	Lannea stuhlmannii	Anacardiaceae	Root
55.	Phytolacca esculenta	Phytolaccaceae	Root
56.	Dysosma pleiantha	Berberidaceae	Root
57.	Morinda citrifolia	Rubiaceae	Root
58.	Astragalus membranaceus	Leguminosae	Root
59.	Epimedium hunanense	Berberidaceae	Aerial parts
60.	Epimedium hunanense	Berberidaceae	Aerial parts
61.	Ocotea foetens	Lauraceae	Branchlets
62.	Maytenus canariensis	Celastraceae	Fruit juice

63.	Euphorbia prolifera	Euphorbiacaeae	Latex
64.	Scirpus holoschoenus	Cyperaceae	Inflorescence
65.	Hypoxis rooperii	Hypoxiaceae	Tuber
66.	Inula linariaefolia	Compositae	Flowers
67.	Ziziphus mauritiana	Rhamnaceae	Stem bark and Fruit
68.	Epimedium hunanense	Berberidaceae	Aerial parts
69.	Cyathea fauriei	Cyatheaceae	Shoot
70.	Fissistigma oldhamii	Annonaceae	Stem
71.	Monnina obtusifolia	Polygalaceae	Aerial parts
72.	Salvia plebeian	Labiatae	Aerial
73.	Matricaria chamomilla	Asteraceae	Flower
74.	Melastoma malabathricum	Melatomataceae	Flower
75.	Carapa guianensis	Meliaceae	Seed oil
76.	Swietenia humilis	Meliaceae	Seed
77.	Ficus pretoiae	Moraceae	Sap
78.	Croton lechleri	Euphorbiacaeae	Latex
79.	Coriolus versicolor	Polyporaceae	Fruitbody
80.	Ipomea batata	Convolvulaceae	Rhizome
81.	Uncaria tomentosa	Rubiaceae	Bark
82.	Ruellia tuberose	Acanthaceae	Bark
83.	Ganoderma lucidum	Ganodermataceae	Fruitbody
84.	Epimedium hunanense	Berberidaceae	Aerial parts
85.	Ligustrum lucidum	Oleaceae	Seed
86.	Pinus parviflora	Pinaceae	Strobilus
87.	Alnus japonica	Betulaceae	Wood
88.	Dillenia suffruticosa	Dilleniaceae	Fruit
89.	Acacia xanthophloea	Leguminosae	Fruit
90.	Deeringia amaranthoides	Amaranthaceae	Fruit
91.	Hippophae salicifolia	Elaeagnaceae	Fruit
92.	Thapsia garganica	Apiaceae	Fruit
93.	Plicosepalus sagittifolius	Loranthaceae	Branches
94.	Maytenus macrocarpa	Celastraceae	Stembark
95.	Knema tenuinervia	Myristicaceae	Stembark
96.	Aphanamixis polystachya	Meliaceae	Stembark
97.	Dysoxylum binectariferum	Meliaceae	Stem bark
98.	Hypoxis nyasica	Hypoxiaceae	Rhizome

Dietary source of anti cancer agents

The cancers can be suppressed by dietary agents like fruits,vegetables and spices.. 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) 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.generally inflammation leads to initiation of carcinogenesis,these dietary agents suppress the inflammatory process that ultimately supree the carcinogenesis.Compounds in the diet can alter the levels of antioxidants by acting as pro-oxidants[39]. Here, consuming the compound causes oxidative stress, which the body responds to by inducing higher levels of antioxidant defenses such as antioxidant enzymes. Compounds like isothiocyanates and curcumin block the transformation of abnormal cells to cancer cells or sometimes kills even existing cancer cells.

Table 3
Dietary sources as anticancer agent.

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

CONCLUSION

Naturevolution mens change in inherited characteristics in biological population throughout successive generations.Evolutionary process leads to diversity in species,individual organisms and even in molecules such as DNA and proreins. Natural products have been a primary source for the treatment of many forms of cancer, many of which are consumed daily with the diet. Natural treatment provides protection against various cancers and many other diseases. Almost all natural products has its own antioxidant medicinal plants and their products prevent from the cancer and other diseases by protecting cells from damage. Thus,by taking diet containing more antioxidants such as fruits,vegetables and herbs produce 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 activity.

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