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Review

Anticancer Natural Products: A Review

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ABSTRACT

Historically, natural products played a forceful role in human treatment ailments. Nowadays, natural products include a large part of current pharmaceutical agents, mostly in the field of cancer therapy. The main aim of this review is to provide a comprehensive summary of the most known natural product used as anticancer globally, including various other natural products. Many of these natural product appears to act through an anticancer mechanism. Overall, natural product research is a vigorous tool to discover novel biologically active components with unique mechanisms of action. Given the diversity of nature, it is sensible to indicate that chemical leads can be produced that are able to interact with most therapeutic targets. This review creates a solid foundation for further study these natural products with additional research and study.

Keywords
Anticancer; Natural product; Plant compounds; Marine flora; Microorganisms; Venom.

INTRODUCTION

Cancer is a serous global health problem responsible for millions of deaths all over the world. It is responsible for approximately 7.6 million deaths worldwide, which is expected to increase to 13.1 million by 2030.[1] Despite the progress in the field of cancer research, still there is a need to discover and develop anti-cancer therapeutic agents. Since long it has been recognized that, natural products represent the richest source of high chemical diversity, providing the basis for identification of novel scaffold structures that serves as starting points for rational drug design.[1] This can be one of the reasons that efforts have been directed to discover promising cancer therapeutic agents from natural sources. Over the years, many natural product-based drugs have been introduced in the market.[2] According to a recent review, 49% of drugs were either natural products or their derivatives that are used in cancer treatment.[3] Moreover, between the year 2005 and 2010, nineteen natural product-based drugs have been approved, among which seven have been classified as natural product, ten as semi-synthetic natural product and two as natural product-derived drugs.[4] Of these, five drugs, everolimus, temsirolimus, ixabepilone, trabectedin and romidepsin, have been developed in the feild of oncology from 2007 to 2009.[1]

Natural products comprise any substance produced by life organism. Mostly, these substances are of small molecular weight (<3,000 Daltons) and of considerable structural diversity. Over 40-years, natural products played a powerful role as established cancer chemotherapeutic agents, either in their naturally occurring forms or their synthetically modified forms.[5] For example, antitumor antibiotics from microbes include the anthracyclines (such as doxorubicin), bleomycin, dactinomycin (actinomycin), and mitomycin C. In turn, members of four classes of plant-derived compounds are used widely as antitumor agents, namely, the bisindole (vinca) alkaloids, the camptothecins, the epipodophyllotoxins, and the taxanes.[6] In addition, there are several examples of promising natural product-derived antineoplastic agents currently in advanced clinical development or recently approved, not only from microbes (e.g., the epothilones and the enediynes) and plants (e.g., the combretastatin and homoharringtonine analogs), but also of marine origin (e.g., the bryostatins, ecteinascidin 743, kahalalide F).[5] Of a total of 155 anticancer agents approved for use in Western medicine and Japan since the 1940s, 47% were classified as either natural products (14%) semi-synthetic derivatives of natural products (28%), or otherwise derived from natural products (5%).[5] Among the largest groups of taxonomically identified classes of organisms that may be studied as sources of new anticancer drugs are arthropods, higher plants, and marine

invertebrates.[7] In addition, natural product researchers have examined other taxonomic classes of organisms found all over the world, including algae, bacteria, fungi, and even terrestrial vertebrates.[5] Natural product drug discovery for anticancer agents requires special procedures involved with sample collection, inclusive of the development of "benefit-sharing" agreements with source countries, whether the samples are of marine or terrestrial origin.[8]

There is a tendency for natural product chemists to specialize on the types of organisms they work, such higher plants or marine fauna, due to the different methods of organism collection and work-up in the laboratory.[5] However, there is increasing evidence that the same secondary metabolite of significance as a potential anticancer agent may be produced by more than one type of organism.[9]

Plant Compounds with Anticancer Properties

The plant based drug discovery give rise to the development of anticancer agents, including plants (paclitaxel, etoposide, camptothecin, vinblastine, vincristine, topotecan, and irinotecan). Beside this there is various agents identified from fruits and vegetables can used in anticancer therapy (Table 1) include spices yielding biologically active components such as curcumin, lycopene, saponins, isoflavones, cucurbitacins, phytosterols, resveratrol, and others.[10] There are compounds which have been identified and extracted from terrestrial plants for their anticancer properties include alvaradoin E (bioactivity-directed fractionation of an extract of the leaves of alvaradoa haitiensis Urb. (picramniaceae).[11] Pancratistatin 3,4-O-cyclic phosphate sodium salt (pancratistatin, a phenanthridone alkaloid, from the bulbs of the plant *Pancratium littorale Jacq*. (Amaryllidaceae)).[12] Polyphenolic compounds include (flavonoids which constitute a large family of plant secondary metabolites as anthocyanins, flavones, flavonols and chalcones[13]; tannins[14]; curcumin[15]; Resveratrol which found in foods including peanuts and grapes and red wine[16] and gallacatechins which present in green tea.[17] Brassinosteroids are naturally occurring compounds found in plants which have role in hormone signalling to regulate growth and cell differentiation, stem and root cells elongation and other roles such as tolerance against disease and stress.[17]

Table 1. *List of Important Anticancer Plant Compounds and Its Mechanism of Action*[18]

S. No.	Scientific Name	Administration of Drug (Compound/Crude Extract) to Experimental Model	Mechanism of Action
1	*Acacia catechu (L.f.) Willd.*	100 µg /ml of catechin rich extract (AQCE) was used against MCF-7 (Human breast adenocarcinoma cellline)	Down regulation of NF-κB and AP-1 expression (cell differentiation and proliferation). Decreases c-jun expression
		10-100 µg /mL of 70% methanolic extract (ACME) from heartwood acts against 7, 12-di methyl benz[a] anthracene induced mammary carcinoma in Balb/c mice.	Induces cell cycle arrest at subG1 phase by increasing Bax/Bcl2 ratio and activating caspase cascade which leads to the cleavage of poly adeno ribose polymerase (PARP)-intrinsic pathway
2	*Allamanda cathartica L.*	Allamandin, β-amyrin, plumericin, isoplumericin, β sitosterol and ursolic acid from leaves through molecular docking	Inhibit cyclin dependent kinases (CDK1) protein regulates cell cycle
3	*Aloe barbadensis Miller.*	200 µmol/L of aloin from leaves was used against HUVECs (human umbilical vein endothelial cells) and SW620 (human colorectal cancer cells)with the dosage of 20 µmol/L	Apotosis and anti-angiogenesis: Suppresses activation of VEGF receptor (VEGFR) 2 mediated c-src and JAK2. Phosphorylation of STAT3 in endothelial cells. Down-regulates activated STAT3 protein, expression of STAT3-regulated antiapoptotic (Bcl-xL), proliferative (c-Myc) proteins.
4	*Anisomeles indica L.*	40 µM of ovatodiolide against renal cell carcinoma	Inhibits β-catenin signaling
		500 µg/mL of aqueous extract from whole plants and 30 µM apigenin was used against 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced MCF-7 cells (Human breast adenocarcinoma)	Anti-metastasis, anti- migration and anti- invasion: Downregulates matrix metalloproteinase (MMP)-9 enzymatic activities, mRNA expression, nuclear factor (NF)-κB subunit p65 and activator protein (AP)-1 subunit c-Fos proteins expression in nucleus
		10, 20 and 40 µM of ovatodiolide from whole plant were used against MDA-MB-231[73]	Cancer cell growth inhibition and proliferation: Prevents phosphorylation of upstream signal IκB kinase. It also suppresses activation of c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, phosphatidylinositol 3-kinase and Akt
5	*Bauhinia racemosa L.*	Methanol extract from stem bark used against N-nitrosodiethyl amine (NDEA) induced hepato carcinogenesis in wister albino rats	Chemoprevention: It suppresses nodule development or hepato cellular lesion formation. It decreases lipid peroxidation and enhances antioxidants levels by reducing the formation of free radicals.
		50, 100 and 200 mg/kg of methanolic extract from stem bark against ehrlich ascites carcinoma (EAC) in swiss albinomice	Before treating drug: Increased level of serum enzymes, bilirubin and decreased protein and uric acid level. Elevated amount of MDA (malondialdehyde) decreased level of antioxidants.
6	*Bauhinia variegata L.*	Ethanol extract from bark and stem were used against HeLa, Dalton's ascetic lymphoma, leukemia and ovariancancer	Arrest G0/G1 phase
7	*Butea monosperma L.*	100 mg/kg and 25 mg/kg of aqueous extract from flower acts against Huh7 and HepG2 cells (hepatoma cells)	Arrest in G1 phase down-regulates MAP kinase and SAPK/JNK signaling pathways
8	*Cajanus cajan L.*	15 or 30 mg/kg of cajanin stilbene acid was used against MCF-7	Induce G2M arrest and apoptosis by activating the mitochondrialpathway
		64 µM of cajanol (5-hydroxy-3-(4-hydroxy-2- methoxyphenyl)-7-methoxychroman-4-one) from root	ROS-mediated mitochondria-dependent pathway induces G_2/M phase and apoptosis inhibits expression of Bcl-2 and induction bax expression leads to activation of caspase-9 and caspase-3 cascade, which is involved in PARPcleavage

9	*Calotropis gigantea L.*	1, 5 and 10 nM of cardenolides and calotropin from root bark used against DLD1, HCT116 and SW480 99	Phosphorylation and degradation of β-catenin by casein kinase 1α inhibits Wnt signaling.
10	*Cardiospermum halicacabum L.*	< 20 µg/ml of n-hexane extract from seeds was used against MCF-7 (Breast cancer cell line)	Anti-proliferative activity
11	*Cissus quadrangularis Linn.*	Acetone extract from stem used against A431 (Human skin epidermoid carcinoma) cellline[21]	Bax–Bcl2 ratio, release of cytochrome c from mitochondria to cytoplasm, cleavage of PARP
12	*Curcuma zedoaria C.*	500 mg/kg of isocurcumenol was used for A549 (Lung carcinoma), KB (nasopharyngeal carcinoma), K562 (leukemic), daltons lymphoma ascitescells	Immuno modulation, immuno stimulation, effects on humoral immune response, anti-angioneogenesis activity
		400 µM of α-curcumene from Rhizome acts against SiHa cells (Human ovarian cancer)	Mitochondrial cytochrome c complex with Apaf-1 and pro-form of caspase-9 activates caspase-3 and caspase-9.
13	*Dioscorea bulbifera L.*	30 mg/ml of ethyl acetate soluble fraction of 75% ethanol extract of the rhizomes was acts against JB6 (Mouse epidermal) cell lines induced by 12-O-tetra de canoylphorbol-13-acetate (TPA)	Onco-protein kinase activation and reactive oxygen burst
14	*Drosera indica L.*	250, 500 mg/kg of ethanol and 500 mg/kg of aqueous extract from whole plant used against dalton lymphoma ascites (DLA) cells in male and female adult swiss albino mice	Increases caspase-3 activity and decreases DNA, RNA and protein content. Cell growth inhibition through antioxidant property
		250 mcg/ml ethanol and aqueous extract was used against ehrlich ascitic carcinoma (EAC) cell line	Anti tumour: Lactate dehydrogenase (LDH) leakage and increased scavenging effect
15	*Elephantopus scaber L.*	25, 50, 100 and 200 µg/ml dichloromethane fraction from whole plant was act against HeLa (cervical), A549 (lung), MCF7 (breast) and Caco2 (colon)	Apoptosis: Enhanced sub G0 content and micronuclei formation. Genotoxicity. Inhibited MDR transporters (ABCB1 and ABC G2)
16	*Embelia ribes Burm.*	10-30 µM of embelin from fruits used against MCF7	Reduction in TNF-α and synthesized as pro- TNF-α then released to extra cellular space by TNF-α converting enzyme.
		Embelin from fruits used for molecular docking (breast cancer cells)	Inactivation of metastatic signaling: MMPs,VEGF and hnRNP-K transcriptional attenuation of mortalin and activation of p53
17	*Gymnema sylvestre R.Br*	121µg and 250 µg of aqueous extract from leaves was used against Hep2 (Liver cancer) cells	Anti-proliferation: Increases intracellular ROS levels
18	*Jatropha gossypifolia L.*	10 µg/ml of whole plant ethanolic extract acts against MCF-7 (Breast cancer cells)	Pro-apoptotic and anti-adhesive effects: Decreases β1- integrin expression and phosphorylation of the focal adhesion kinase at Tyr397
19	*Kaempferia galanga L.*	Ethyl p methoxy cinnamate from Rhizome was used against HepG2 cells (Human hepatocellular liver carcinoma)	Apoptotic induction and inhibition of proliferation: Increase subG0 cell population
20	*Kaempferia rotunda L.*	500 mg/Kg of chloroform extract and 20 mg/Kg of pinostrobin from Rhizome acts against T47D (Human breast cancer cell lines)	Suppress c-Myc expression
21	*Lantana camara L.*	15 mM of pentacyclic triter penoids-reduced Lantadenes A and B used against HL-60 cells.	Induction of apoptosis: Suppresses the production of nitrite, TNF-α and iNOS gene expression
		20, 40, 80 mg/kg of Ursolic acid stearoyl glucoside act against Induced hepato cellular carcinoma in wistar rats by diethylnitrosamine (DENA).	It suppresses free radical formation by scavenging the hydroxyl radicals. Modulates the level of lipid peroxidation and increases the endogenous antioxidant enzymes level
		30 µg/mL of ethanolic extract from Leaves act against MCF-7 (Human breast cancer cell line)	Bid and bax was increased and Bcl-2 was decreased after drug treatment. It also modulates cleavage of caspase-8, caspase-9 and poly (ADP-ribose) polymerase(PARP)
22	*Lawsonia inermis L.*	30 µg/ml-1 of leaves chloroform extract act against Hep2 cells and Caco2 (colon)	Down regulation of c-myc expression
		180 mg/kg of ethanolic crude extract from root was used against Dalton's lymphoma ascites.	Enhances the activities of catalase, glutathione peroxidase and glutathione S transferase and increases vitamin C, E and reduced glutathione level.
23	*Leea indica Burm.*	40 mg/kg/day of methanolic extract acts against ehrlich ascites carcinoma (EAC) cells in swiss albino mice	cytotoxicity
		60 µM of mollic acid arabinoside was used against Ca Ski cervical cancer cells	Induce mitochondrial mediated apoptosis
		60 µM of mollic acid xyloside (MAX) from leaves against Ca Ski cervical cancer cells	Decreases the expression of proliferative cell nuclear antigen, increases sub-G1 cells and arrest cells in S and G2/M phases
		500 and 1000 µg/mL of ethyl acetate fraction was used against Ca Ski cellline	Inducing apoptosis: Accumulation of sub-G1 cells, depletion of intracellular glutathione and activation of caspase-3.
24	*Moringa oleifera L. Moringaceae*	50 µg/ml of ethanolic extract from leaves, bark and seed showed activity against MDA-MB-231 and HCT-8 (colorectal)	Anti-malignant properties: Arrest cell
		50-400 µg/ml of leaf extract against HepG2 (Hepato cellular carcinoma cells) and A549 non-small cell lung cancer	Anti-proliferation and apoptosis
25	*Oroxylum Indicum L.*	20 µM of baicalein from stem bark against CT-26 (colon carcinoma)	Inhibit activation of pro-PDGF-A, B and pro-VEGF C
26	*Oxalis corniculata Linn.*	100 and 400 mg/kg of Ethanolic extract from Whole plant for Ehrlich ascites carcinoma (EAC)-induced in swiss albino mice	Antitumor and antioxidant activity: Increase intotalprotein, albumincontent,catalaseand reduced glutathione levels. Decrease in AST, ALT and ALP contents, liver MDA level

27	*Physalis minima L.*	25-100 g/ml of chloroform extract from whole plant was used against NCI-H23 (Human lung adenocarcinoma)	Inhibit cell proliferation and induce apoptosis: Activation of c-myc, caspase-3 and p53 gene expression
		6.25 µg/mL of Physalin F used against T-47D cells (Human breast carcinoma)	Chemoprevention / apoptosis: Activation of caspase-3 and c-myc pathways due to the presence of cyclo hexanone and epoxy moieties.
		25-100 g/ml of chloroform extract from whole plant act against Caov-3 (Human ovarian carcinoma)	Apoptosis and autophagy
28	*Polyalthia longifolia Sonn.*	50 µg/ml of was chloroform extract from Leaves against HL-60	Induce intrinsic or mitochondrial-dependent apoptotic pathway
29	*Tecomella undulate D.*	30 µg/ml of undulatoside-A, undulatoside-B and tecomin from bark acts against K562 (chronic myeloid leukemia cells)	Cell cycle arrest at S phase, increase in Annexin V positive cells. Increase in FAS, FADD levels and activation of caspase 8 and 3/7
30	*Terminalia chebula R.*	100 µl of chebulagic acid from fruits showed apoptosis in COLO-205 cells	Inhibition activity of COX and 5-LOX
31	*Tinospora cordifolia T.*	100 and 200 mg/kg of palmatine (alkaloid) from stem against 7,12-dimethylbenz(a) anthracene (DMBA) induced skin carcino genesis in swiss albino mice.	Antioxidant and chemo-preventive activity
		100 µl of Hexane fraction act against EAT (Ehrlich ascites tumor).	Apoptosis signals activates caspase-8, its substrate BID protein releases cytochrome C to bind Apaf-1 which induces auto-activation of caspase-9, which in turn activates caspase-3. It cleaves poly-ADP-ribose polymerase, lamins and inhibitor of caspase activated DNase (ICAD).
32	*Triumfetta rhomboidea Jacq. (Tiliaceae)*	100 and 200 mg/ kg of leaves methanolic extract used against ehrlich ascites carcinoma (EAC) DLA bearing male swiss albino mice.	Antitumor and antioxidant activity: Decreases the level of lipid peroxidation and increases glutathione (GSH), superoxide dismutase (SOD) and catalase level
33	*Urginea indica Roxb.*	75 µgml-1 of Glycoprotein from bulbs act against HUVECs and EAT cells in swiss albino mice	Antiangiogenic and proapoptotic activity: Inhibition of translocation of nuclear factor kappa B to the nucleus thus decreases the expression of vascular endothelial growth factor gene
34	*Vitex negundo L. (Verbenaceae)*	10 µg/mL of chrysoplenetin and chrysosplenol D used against PANC-1 (Human pancreatic cancer) cells, NCI-H522 (lung), OVCAR-3 (ovarian) and PC-3 (prostate) cells.	Cytotoxicity and apoptotic morphological changes (DNA fragmentation, nuclear condensation and membrane blebbing)
		4 to 6 µg/mL of vitexin from i) Fruit iii) Seeds used against COC1 (ovarian cancer cells) and MDA-MB-231154	Apoptosis by caspase activates poly (ADP ribose) polymerase (PARP) and cleaved into a COOH-terminal fragment

Table 2. *Anticancer Compounds from Marine Environment*[22]

No	Name of the Compound	Source of Organisms	Chemical Class	Cancer Target
1	Arenamides A–C	Actinomycete (*Salinispora arenicola*)	Cyclohexa-depsipeptides	Human colon carcinoma cell line (HCT-116)
2	Heteronemin	Sponge (*Hyrtios sp.*)	Sesterterpene	Leukemia (K562 cells)
3	6-bromoisatin	Whelk (*Dicathais orbita*)	Indole derivative	Ovary, granulosa, Choriocarcinoma (OVCAR-3, KGN, Jar)
4	Tyrindoleninone	Whelk (*Dicathais orbita*)	Indole derivative	Ovary, granulosa, Choriocarcinoma (OVCAR-3, KGN, Jar)
5	Cryptosphaerolide	Ascomycete fungal strain CNL-523 (*Cryptosphaeria sp.*)	Sesquiterpenoid	Human colon carcinoma cell line (HCT-116)
6	Makaluvamine A	sponge (*Zyzzya fuliginosa*)	Pyrroloquinoline	Colon cancer (HCT-116 cells)
7	Ascididemin	Actinomycete (*Salinispora arenicola*)	Cyclohexa-depsipeptides	Human colon carcinoma cell line (HCT-116)
8	Lamellarin D	Prosobranch mollusc of the genus (*Lamellaria*)	Alkaloid	Leukemia
9	Spongistatin 1	Sponges (*Spirastrella spinispirulifera and Hyrtios erecta*)	Macrocyclic lactone	Leukemia (Jurkat cells)
10	Streptochlorin	*Streptomyces sp.*	Methyl pyridine	Leukemia (U937 cells)

Anticancer Compound from Marine Flora

Marine floras include microflora (bacteria, actinobacteria, cyanobacteria and fungi, microalgae, macroalgae, and flowering plants (mangroves and other halophytes) contain a massive number of natural products and novel chemical structures with unique activities that may be useful in finding the potential drugs with major efficacy and specificity forhuman treatment[19] (Table 2). The marine organisms produce novel chemicals to withstand extreme variations in their environment, and the chemicals produced are unique in diversity, structural, and functional features.[20] Mostly invertebrates that include sponges, soft corals, sea fans, sea hares, nudibranchs, bryozoans, and tunicates are proven to be the potent sources of drugs.[21] It is now believed that microbial flora present in the invertebrates are responsible for the production of medicinal compounds. Marine floras are rich in biologically active and medicinally potent chemicals as polyphenols, polysaccharides and alkaloids are the most predominant group of compounds which are applicable for antioxidant and anticancer activities.[19]

Table 3. *Some Examples of Bacterial Strains with Bioactivity and the Sources where they were Obtained*[26]

Bacteria	Gram (+ or -)	Activity	Target organism	Disease
Pseudomonas bromoutilis	-	Anticancer	*Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes*	Pneumonia, osteitis, arthritis, endocarditis, localized abscesses
Chromobacteria marinum	-	Antibacterial	*Escherichia coli, Pseudomona aureginosa, Staphylococcus aureus*	Pneumonia, osteitis, arthritis, endocarditis, localized abscesses
Flavobacteria uliginosum	-	Anticancer	Sarcoma-180 cells	Viral tumor
Bacillus sp.	+	Anticancer	HCT-116 cells	Colorectal Cancer
Lactococcus lactis	+	Anticancer	Human papilloma virus type 16(HPV-16)	Colorectal Cancer
Staphylococcus aureoverticillatus	+	Anticancer	Tumor cells	Tumors
Marinobacter drocarbonoclasticus	-	Antibacterial (siderofore)	*Mycobacteria tuberculosis, Bacillus anthracis*	Tuberculosis, carbuncle (anthraxlike)

Marine bacteria: Produce secondary metabolites which have anticancer agents (e.g., eleutherobin, discodermolide, bryostatins, and sarcodictyin)[23] as in Table 3. Most of marine bacteria produces toxins which are useful in neurophysiological and neuropharmacological studies.[24] Only a few marine bacteria can be isolated under laboratory conditions and there is an urgent need to isolate the bacteria that produce unique and novel natural products.[25]

Marine actinomycetes: Received very recent attention. Gutingimycin is a highly polar trioxacarcin derivative from streptomyces species, isolated from sediment of the Laguna de Terminos, Gulf of Mexico.[19] The same Streptomyces species also yields trioxacarcins D-F, in addition to the known trioxacarcins A-C. Among the antibiotic-producing microbes, marine actinomycetes within the family micromonosporaceae are very promising.[27] These microbes revealed to be a promising sources of anticanceragents that target proteasome function.

Thiocoraline is a novel bioactive depsipeptide isolated from *Micromonospora marine*, a microorganism located in the mozambique strait that inhibits ribonucleic acid (RNA) synthesis.[28]

Marine fungi: Marine fungi are least studied than terrestrial fungi. Obligate marine fungi are still an unexplored resource, although, marine facultative fungi, have been studied due to their production of new metabolites which are not found in terrestrial fungi.[29] Recently more interest has been generated on studying biologically active metabolites from higher fungi (basidiomycetes), endophytic fungi and filamentous fungi from marine habitats, the symbiotic lichens on its anticancer activity.[30]

Marinemacro algae (Cyanobacteria): Marinemicro algae is one of the potential organisms which can be the richest sources of potent bioactive compounds including toxins with potential for pharmaceutical applications.[31] More than 50% of the marine cyanobacteria are potentially exploitable for extracting bioactive substances which are effective in killing the cancer cells.[19] Scytonemin is a protein serine/threonine kinase inhibitor isolated from the cyanobacterium *Stigonema sp.* and this compound is a yellow-green ultraviolet sunscreen pigment, known to be present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae.[23] Largazole derived from *Symploca sp.* is a novel chemical scaffold with fabulous antiproliferative activity.[19] Other compounds, apratoxin A, isolated from a strain of Lyngbya boulloni,[32] coibamide A derived from a strain of Leptolyngbya,[33] curacin-A, isolated from the organic extracts of curacao collections of Lyngbya majuscule.[34]

Marine macro algae (Seaweed): Marinemacro algae many researchers have worked on the antioxidant, antitumor, and immunomodulating activities of seaweeds as edible seaweed like *Palmaria palmate*,[35] the alcoholic extract of the red alga *Acanthophora spicifera*,[36] the seaweeds *Acanthaphora spicifera*,[37] *Ulva reticulate*,[38] *Gracilaria foliifera*,[39] the brown seaweed *Sargassum thunbergii*,[40] fucoidan from *Ascophyllum nodosum*,[41] stylopoldione from *Stypodium sp.*,[19] condriamide-A from *Chondria sp.*,[42] caulerpenyne from *caulerpa sp.*,[43] two compounds meroterpenes and usneoidone isolated from *Cystophora sp.*,[44] phloroglucinol and its polymers namely eckol (a trimer),[45] *phlorofucofuroeckol* A (a pentamer),[45] dieckol and 8,8'-bieckol (hexamers) isolated from the brown alga eisenia bicyclis and padina[45] owing to their biological properties.

Mangroves and other higher marine plants: Mangroves have long been used in fisher-folk medicine to treat diseases. Based on traditional knowledge and preliminary scientific work, sixteen higher marine plants considered asa source of anticancer drugs[19] (Table 4). A sulphur containing alkaloid, 1,2-dithiolane (brugine) isolated form *Bruguiera sexangula*, ribose derivative of 2-Benzoxazoline isolated from *Acanthus ilicifolius* and tea from the mangrove plant *Ceriops decandra* has shown anticancer activity.[46]

Microorganisms with Anticancer Properties

Small organic molecules derived naturally from microorganisms have provided a number of beneficial cancer chemotherapeutic drugs.[5] Introduce microorganisms into the body leads to the activation of various immune mechanisms, which manifests itself in increasing the number and recruitment of congenital immune cells, activation of acquired immunity cells, and production of proinflammatory cytokine.[48] It is assumed that the rallied immune system, by intentionally introducing microorganisms into the oncological patient, is able to at least limit the development

Table 4. *List of Anticancer Compounds Isolated from Endophytic Fungi from Mangrove Habitats*[47]

No	Host Plant	Fungal Endophyte	Isolated Cytotoxic Compound/s	Tested Cell Line/s	Cytotoxicity
1	*Excoecaria agallocha*	*Phomopsis sp.* ZSU-H76	2-(7'-hydroxyoxooctyl)-3-hydroxy-5-methoxybenzeneacetic acid ethyl ester	HEp2	25
				HepG2	30
2	*Rhizophora mucronata*	*Pestalotiopsis sp.*	Cytosporones J-N	L5178Y	Not Active up to 10 μg/mL
			Pestalasins A-E	HeLa	
			Pestalotiopsoid A	PC12	
3	*Rhizophora mucronata*	*Pestalotiopsis sp.*	Pestalotiopsone A	L5178Y	NA
			Pestalotiopsone B		NA
			Pestalotiopsone C		NA
			Pestalotiopsone D		NA
			Pestalotiopsone E		NA
			Pestalotiopsone F		26.89
4	*Not mentioned*	*Mangrove endophytic fungus No. ZSU44*	Secalonic acid D	HL60	0.38
				K562	0.43
5	*Excoecaria agallocha*	*Pestalotiopsis sp.*	Phomopsis-H76 A	KB	Allthecompoundsare
			Phomopsis-H76 B	KBv200	Inactiveagainstallthe
			Phomopsis-H76 C	MCF7	Tested cell lines
6	*Kandelia woody tissue*	*Halorosellinia sp.* *Guignardia sp.*	1-hydroxy-3-methyl anthracene-9,10-dione	KB	3.17
				KBv200	3.21
7	*Sonneratia apetala*	Zh6-B1 (unidentified)	3R,5R-Sonnerlactone	KV/MDR	42.4
			3R,5S-Sonnerlactone		41.6
8	*Xylocarpus granatum*	XG8D (unidentified)	Merulin A	BT474	4.98
				SW620	4.84
			Merulin B	BT474	>10
				SW620	>10
			Merulin C	BT474	1.57
				SW620	4.11
9	*Acanthus ilicifolius*	*Pestalotiopsis sp.*	Penicinoline	95-D	0.57
				HepG2	6.5
				HeLa	>100
				KB	>100
				KBv200	>100
				HEp2	>100
10	*Unidentified mangrove (Taiwan Strait)*	*Pestalotiopsis sp.*	Paeciloxocins A	HepG2	1
			Paeciloxocins B		65
11	*Excoecaria agallocha*	*Penicillium expansum*	Expansols A	A549	NR
				HL-60	15.7
			Expansols B	A549	1.9
				HL-60	5.4
12	*Kandelia candel*	*Fusarium sp.*	5-O-methyl-2'-methoxy-3'-methylalpinumisoflavone	HEp2	4
				HepG2	11
13	*Aegiceras corniculatum*	*Alternaria sp. ZJ9-6B*	Alterporriol K	MDA-MB-435	26.97
			Alterporriol L	MDA-MB-435	13.11
14	*Rhizophora mucronata*	*Irpex hynoides*	Ethyl acetate extract	HEp2	125
15	*Rhizophora annamalayan*	*Fusarium oxysporum*	Taxol	NT	NT
16	*Bruguiera gymnorrhiza*	*Rhytidhysteron rufulum*	Rhytidchromones A	MCF7	19.3

Compounds are included in the column"isolatedcompound/s". NA-Not Active; NR-Not Reported; NT-Nottested

of cancer.[49] This is a method in which microbes indirectly lead to cancer regression especially in those in whom other commonly used treatments have failed.

Bacteria: Bacteria can be applied in various forms for therapeutic purposes. Apart from the whole, living attenuated cells, we can use genetically engineered bacteria expressing particularly desirable factors.[50] Microorganisms are also applied as vectors, which are carriers of specific chemotherapeutics agents or enzymes useful in thedestruction of cancer cell. This method allows a significant reduction of the side effects of treatment that usually accompany traditional chemotherapy.[51] Moreover, there is a therapeutic potential to use bacterial secretion, for example, toxins.[52] Their presence in the tumor environment could have destruct the cancer cells. The use of sporangial bacteria, which can survive under unfavorable environmental conditions, represents another approach, which has been applied in the experiments with *Clostridium novyi*. This microorganism prefers anaerobic conditions, which are found in the tumor.[53] Instead of spreading over the entire organism, the bacteria are directed to the tumor site only, where they have the optimal conditions for growth.[54] This bacterial property allows the patient to be protected against the development of serious infections. From the bacteria that used in cancer therapy (*Mycobacterium bovis* BCG is a strain of mycobacterium bovis developed by Albert Calmett and Camille Guérin as a tuberculosis vaccine[55]; *Streptococcus pyogenes OK-432*[56]; *Clostridium novyi*[57]; *Salmonella enterica*[50]; serovar typhimurium which is obligate anaerobes and facultative anaerobes[58]; *Clostridium histolyticum*[59]; *Magnetococcus marinus* MC1 is a gram-negative cocci found in the Atlantic Ocean near Rhode Island, USA.[60]

Toxoplasma gondii: Toxoplasma gondii is an obligatory intracellularparasite.[61] It is life-threatening to people with impaired immunity or pregnant women, who can suffer abortion or birth malformation. It turns out that the protozoan and its lysate, toxoplasma lysate antigen, can be used to treat cancer.[60]

Plasmodium falciparum: Plasmodium falciparum (Malaria) caused by *Plasmodium sp.*, is one of the most common parasitic diseases in the world.[62] *Plasmodium falciparum* is considered to be the most malignant causative agent of malaria because it aggregates erythrocytes and thrombocytes that adhere to the vascular endothelium, which can lead to the closure of vascular light and thus damage to vascular walls and even necrosis. However, despite all the negative features of the parasite, it can be used to treat cancer.[63]

Natural Product with Anticancer Activity from Terrestrial Vertebrate and Invertebrate

Mammals and milk: Natural product isolated from mammal source is poorly studied, throughout screening for the review little data were available. Ryan et al[64] described four bovine meat-derived peptides that inhibit angiotensin-converting enzyme (ACE) and also exhibit anti-proliferative activity. A number of studies have reported the anticancer effects of milk protein-derived peptides on various cancer cells as the casein fraction-derived caseinophosphopeptides (CPPs) and lactoferrin is an 80-kDa iron-binding glycoprotein that belongs to the transferrin family.[65]

Amphibians: Amphibians skin secretions contain a wide range of biologically active compounds and have garnered attention due to their potential for drug development.[66] Moreover, the Chinese traditionally administered secretions from frog skin and toad parotid glands for medicinal purposes since ancient times. Hundreds of those peptides have been identified since the discovery of the first antimicrobial peptide from amphibian skin. Some of the naturally occurring amphibian skin peptides and their analogs proven to be cytotoxic to tumor cells only and are promising anticancer agents for example, Alyteserin-2a, isolated from the midwife toad (*Alytes obstetricans*)[67]; ascaphin-8 and XT-7 peptides obtained from the skin secretions of *Ascaphus truei* and *Silurana tropicalis*[68]; aurein peptides from the green and golden bell frog (*Litoria aureus*) and the southern bell frog (*Litoria raniformis*)[69]; dermaseptin B2 and B3,of the dermaseptin family, isolated from the South American tree frog (*Phyllomedusa bicolor*)[70]; dermaseptin L1 and phylloseptin L1, isolated from the lemur leaf frog (*Agalychnis lemur*).[71]

Reptilian: Reptilian peptides derived from crocodiles as the cationic antimicrobial peptides KT2, RT2 and RP9 from *Crocodylus siamensis* leukocyte extract proven to have a great anticancer activity.[72] He et al[73] has reported antitumor peptides T1 and T2 derived from the enzymatic hydrolysates of the Chinese three-striped box turtle (*Cuora trifasciata*).

Animal venoms: Animal venoms and toxins consist of a complex mixture of proteins and peptides and are rich with biologically active peptides with potent anticancer activity.[74] Among venomous animals, scorpions, is a source of peptidyl neurotoxins, which are used as tools to study different ion channels, such as the Na^+, K^+, Ca^+, and Cl^- ion channels[75] (Table 5). Chlorotoxin (CTX) is a small neurotoxin of 36 amino acids that was isolated from the venom *Leiurus quinquestriatus* scorpion. Initially, CTX was used as a pharmacological tool to characterize chloride channels. CTX can target glioma, small cell lung carcinoma, melanoma, neuroblastoma and medulloblastoma cells.[76]

Spider venom contain proteins and peptides including enzymes (such as proteases, phospholipases, andhyaluronidases), neurotoxins, and cytolytic peptides.[77] A short cationic peptide latarcin 2a (Ltc2a) isolated from *Lachesana tarabaevivenom*[78] have anticancer activity.

Venom from bees and wasps is now being studied to design and develop new therapeutic drugs from their venom.[79] Melittin peptide (26 amino acid) isolated from the honey bee *Apis mellifera*, is the most studied and famous bee venom-derived peptide. It inhibits different cancer cells *in vitro*, including leukemic, lung tumor, astrocytoma, glioma, squamous carcinoma,ovarian carcinoma, hepatocellular carcinoma, renal cancer cells, prostate cancer and osteosarcoma.[80] Unfortunately this peptide is toxic to both normal and cancer cells. mastoparan is 14-amino acid cationic peptide isolated from *Vespula lewisii* venom that has shown *in vitro* anticancer activity.[81]

Table 5. *The Anticancer Mechanisms of Some Venomous Peptides and Indirectly Derived Drug*[85]

Target	The Major Mechanisms of Action	Molecular Target	Drug	Drug Class	Indications	Clinical Phase
Ion Channels	The proliferationand invasion of cancer cells	Chloride (Cl^-) channels: CLC3	131I-TM601 (131I-CTX)	Peptide (36aa)	Gliomas	Phase III
			BLZ-100 (ICG-CTX)	Peptide (36aa)	Gliomas tumor marker forsurgery	Phase I
		Sodium (Na+) channels	AGAP	Peptide (66aa)	Colon cancer cells, Malignant glioma cells	Preclinical studies
		Potassium (K+) channels: KV11.1(hERG)	Ergtoxin	peptide (42-62aa)	Ovarian cancer cells	Preclinical studies
		Transient receptor potential(TRP) channels: TRPV6	SOR-C13	peptide(13aa)	Solid tumors with overexpressing the TRPV6 ion channel	Phase I
Integrins	The invasion, migration, angiogenesis, and metastasis of cancer cells	$\alpha_v\beta_3$, $\alpha_v\beta_5$	Cilengitide	Peptidomimetic (5aa)	1 Glioblastoma with methylated MGMT promoter	1 PhaseIII
					2 Glioblastoma with unmethylated MGMTpromoter	2 PhaseII
					3 NSCLC	3 PhaseII
		$\alpha_5\beta_1$	ATN-161	Peptidomimetic	Malignant Glioma	Phase II
		Five integrin receptors ($\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $_v\beta_6$,$\alpha_5\beta_1$)	GLPG0187	Peptidomimetic	Bone metastasis in metastatic breast cancer	Phase I
		$\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_5\beta_1$	Vicrostatin	Peptide(69aa)	Ovarian cancer, Gliomas	Preclinical studies
G protein-coupled receptor	The metastasis of cancer cells	Gastrin-releasing peptide receptor	BAY86-7548	Peptide (14aa)	Prostate cancer imaging	Phase II/III
Membrane molecules	The disruption of cancer cell membrane	Sialic acid-rich glycoproteins, PS and PC, heparansulfate	1 MP1	1 Peptide (14aa)	1 Human leukemic Jurkatcells	Preclinical studies
			2 Melittin	2 Peptide (26aa)	2 Human renal cancer, lung cancer, liver cancer,etc.	
			3 Mastoparan	3 Peptide (14aa)	3 Pancreatic cancer cells	
		Phospholipids	Hemilipin	heterodime	HUVECs and HPAECs	Preclinical studies

Most snake venoms are a mixture of several proteins, peptides, toxins, enzymes and non-protein components.[82] Bioactive peptides from snake venoms have significantly contributed to the treatment of many humandiseases, and some of them may selectively target cancer cell membranes, affecting the proliferation of cancer cells.[83] For example, crotamine, a polypeptide of 42 amino acids isolated from South American rattle snake venom; cathelicidin-BF (BF-30) is a cathelicidin-like polypeptide of 30 amino acids and a natural antibacterial peptide extracted from the venom of the snake *Bungarus fasciatus*; purified L-amino acid oxidases from *Bothrops leucurus* which is toxic to cancer cell.[84]

CONCLUSION

This review aims to boost the use of natural product arising from their anticancer activities. Natural product proven to have efficacy asan anticancer activity already. The mechanism of action of many products has been identified and other still under investigation. Overall, natural product research is a vigorous tool to discover novel biologically active components with unique mechanisms of action. Given the diversity of nature, it is sensible to indicate that chemical leads can be produced that are able to interact with most therapeutic targets. As such, new and efficacious drugs can be developed by way of safety treatment of the cancer diseases and get rid of it.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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