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 serious 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, 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 serve as starting points for rational drug design.2 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.2 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.3 Of these, five drugs, everolimus, temsirolimus, ixabepilone, trabectedin and romidepsin, have been developed in the field of oncology from 2007 to 2009.3

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.4 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%).8 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. 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. 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.

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. 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.

**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, iso flavones, cucurbitacin, phytosterols, resveratrol, and others. There are compounds which have been identified and extracted from terrestrial plants for their anticancer properties include alvaradoin E (biodiversity-directed fractionation of an extract of the leaves of alvarado haitiens Urb. (picramniaceae)), Pancreatistatin 3,4-O-cyclic phosphate sodium salt (pancreatistatin, a phenanthridone alkaloid, from the bulbs of the plant Pancratium littorale Jacq. (Amaryllidaceae)). Polyphenolic compounds include (flavonoids which constitute a large family of plant secondary metabolites as anthocyanins, flavones, flavonols and chalcones; tannins; curcumin; Resveratrol which found in foods including peanuts and grapes and red wine and gallacteacthes which present in green tea). 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.

| Table 1. List of Important Anticancer Plant Compounds and Its Mechanism of Action

| 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 cell line) | 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-dimethyl benz[a] anthracene induced mammary carcinoma in Balb/c mice. | Induces cell cycle arrest at subG1 phase by increasing Bad/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, plumiercin, isoplumericin, β-sitosterol and ursolic acid from leaves through molecular docking | Inhibit cyclin dependent kinases (CDK) protein regulates cell cycle |
| 3     | Aloe barbadensis Miller. | 200 μmol/L of aloe from leaves was used against HUVECs (human umbilical vein endothelial cells) and SW620 (human colorectal cancer cells) with the dosage of 20 μmol/L | Apoptosis and anti-angiogenesis: Suppresses activation of VEGF receptor (VEGFR) 2 mediated e-csrc and JAK2. Phosphorylation of STAT3 in endothelial cells. Down-regulates activated STAT3 protein, expression of STAT3-regulated antipapoptotic (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 nude mice |
| 5     | Bouinavia racemosa L. | Methanol extract from stem bark used against N-nitrosodiethylamine (NDEA) induced hepatic carcinogenesis in wistar albino rats | Chemoprevention: It suppresses nodule development or hepatocellular 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 albino mice | 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     | Bouinavia variegata L. | Ethanol extract from bark and stem were used against Hela, Dalton’s ascitic lymphoma, leukemia and ovarian cancer | 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 G2/M arrest and apoptosis by activating the mitochondrial pathway |
|       |                  | 64 μM of cajanol (5-hydroxy-3-(4-hydroxy-2-methoxyphenyl)-7-methoxy chroman-4-one) from root | ROS-mediated mitochondria-dependent pathway induces G2/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 PARP cleavage |
| No. | Plant Name                     | Description                                                                                           | Activity/Effect                                                                                                 |
|-----|--------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| 9   | Calotropis gigantea L.        | 1.5 and 10 nM of cardenolides and calotropin from root bark used against DLD1, HCT116 and SW480       | 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  | Cassia quadrangularis Linn.   | Acetone extract from stem used against A431 (Human skin epidermoid carcinoma) cell line               | Bax–Bcl2 ratio, release of cytochrome c from mitochondria to cytoplasm, cleavage of PARP.                    |
| 12  | Curcuma zedoaria C.           | 500 μg/kg of isocurcumonol was used for A549 (Lung carcinoma), KB (nasopharyngeal carcinoma), K562   | Immuno modulation, immuno stimulation, effects on humoral immune response, anti-angiogenesis activity.         |
|     |                               | (Leukemic), Dalton's lymphoma ascites cells                                                            |                                                                                                                |
| 13  | Drosera indica L.             | 400 μM of α-curcumin 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.  |
| 14  | Dioscorea bulbifera L.        | 30 μg/mL of ethyl acetate soluble fraction of 75% ethanol extract of the rhizomes was acts against   | Onco-protein kinase activation and reactive oxygen burst                                                    |
|     |                               | J6 (Mouse epidermal) cell lines induced by 12-O-tetradecanoylphorbol-13-acetate (TPA)                 |                                                                                                                |
| 15  | Elephantopus scaber L.        | 250, 500 μg/kg of ethanol and 500 μg/kg of aqueous extract from whole plant used against dalton lymphoma | Anti-tumour: Lactate dehydrogenase (LDH) leakage and increased scavenging effect.                           |
|     |                               | ascites cells (DA) cells in male and female adult Swiss Albino mice                                     |                                                                                                                |
| 16  | Embelia ribes Burm.           | 10 μg/mL of whole plant ethanolic extract acts against MCF-7 (Breast cancer cells)                    | Reduction in TNF-α and synthesized as pro-TNF-α then released to extra cellular space by TNF-α converting enzyme. |
| 17  | Gymnema sylvestre R.Br        | 250 μg/mL of ethanol and aqueous extract was used against ehrlich ascitic carcinoma (EAC) cell line     | Anti-proliferation: Increases intracellular ROS levels                                                       |
| 18  | Jatropha gossypifolia L.       | 12 μg and 250 μg of dichloromethane fraction from whole plant was act against HeLa (cervical), A549   | Apoptosis: Enhanced sub G0 content and micronucleus formation.                                               |
|     |                               | (lung), MCF7 (breast) and Caco2 (colon)                                                               | Genotoxicity. Inhibits MDR transporters (ABCB1 and ABCG2)                                                   |
| 19  | Kaempferia galanga L.         | Embelin from fruits used against MCF7                                                                  | Anti-apoptotic and anti-adhesive effects; Decreases J1-integrin expression and phosphorylation of the focal adhesion kinase at Tyr397 |
| 20  | Kaempferia rotunda L.         | Ethyl p methoxy cinnamate from Rhizome was used against HepG2 cells (Liver cancer) cells              | Apoptotic induction and inhibition of proliferation: Increase subG0 cell population                           |
| 21  | Lantana camara L.             | 15 μM of pentacyclic triterpenoids-reduced Lantadenes A and B used against HL-60 cells                  | Suppress c-Myc expression                                                                                   |
|     |                               | 20, 40, 80 μg/kg of Ursolic acid steroidal glycoside act against Induced hepato cellular carcinoma in   | Induction of apoptosis Suppresses the production of nitrite, TNF-α and iNOS gene expression                   |
|     |                               | wistar rats by diethylthionitrosamine (DENA).                                                         |                                                                                                                |
|     |                               | It suppresses free radical formation by scavenging the hydroxyl radicals. Modulates the level of lipid |                                                                                                                |
|     |                               | peroxidation and increases the endogenous antioxidant enzymes level                                    |                                                                                                                |
| 22  | Lawsonia inermis L.           | 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)                                                          |
| 23  | Leea indica Burm.             | 30 μg/ml-1 of leaves chloroform extract act against Hep2 cells and Caco2 (colon)                       | Down regulation of c-myc expression                                                                          |
|     |                               | 180 μg/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. |
| 24  | Moringa oleifera L.           | 40 μg/kg/day of methanolic extract acts against ehrlich ascites carcinoma (EAC) cells in swiss albino   | Cytotoxicity                                                                                                  |
|     | Moringa oleifera L.           | 60 μM of molic acid arabinoside was used against Ca Ski cervical cancer cells                           | Induce mitochondrial mediated apoptosis                                                                      |
|     | Moringa oleifera L.           | 60 μM of molic 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 G2/M phases |
|     | Moringa oleifera L.           | 500 and 1000 μg/mL of ethyl acetate fraction was used against Ca Ski cell line                          | Inducing apoptosis/Accumulation of sub-G1 cells, depletion of intracellular glutathione and activation of caspase-3. |
| 25  | Oroxylum indicum L.           | 20 μM of bacoside from stem bark against CT-26 (colon carcinoma)                                       | Inhibit activation of pro-PDGF-A, B and pro-VEGF C                                                         |
| 26  | Ocimum cumminum Linn.         | 100 and 400 μg/kg of Ethanolic extract from Whole plant for Ehrlich ascites carcinoma (EAC)-induced in | Antitumor and antioxidant activity: Increase introstatinpro, albumincontent,catalaseand reduced glutathione levels. Decrease in AST,ALT and ALP contents, liver MDA level. |
|     |                               | swiss albino mice                                                                                      |                                                                                                                |
### Table 2. Anticancer Compounds from Marine Environment

| No. | Name of the Compound | Source of Organisms | Chemical Class | Cancer Target |
|-----|----------------------|---------------------|----------------|---------------|
| 1   | Arenamides A–C       | Actinomyces (Salinispora arenicola) | Cyclohexa-depsipeptides | Human colon carcinoma cell line (HCT-116) |
| 2   | Heteronemin          | Sponge (Hyrtox sp.) | Sesquiterpene | Leukemia (K562 cells) |
| 3   | 6-bromoverticillin   | Whelk (Dicathais orbita) | Indole derivative | Ovary, granulosa, Choriocarcinoma (OVCAR-3, KGN, Jr) |
| 4   | Tyritolominine       | Whelk (Dicathais orbita) | Indole derivative | Ovary, granulosa, Choriocarcinoma (OVCAR-3, KGN, Jr) |
| 5   | Cryptosphaerolide    | Ascomycete fungal strain CNL-523 (Cryptosphaerida) | Sesquiterpenoid | Human colon carcinoma cell line (HCT-116) |
| 6   | Makaluvamine A       | Sponge (Zyzyx zeylanica) | Pyrrrolequinoline | Colon cancer (HCT-116) |
| 7   | Ascididemin          | Actinomyces (Salinispora arenicola) | Cyclohexa-depsipeptides | Human colon carcinoma cell line (HCT-116) |
| 8   | Lamellaria D         | Prosobranch mollusc of the genus (Lamellaria) | Alkaloid | Leukemia |
| 9   | Spongistatin I       | Sponges (Spinastrella spinaturra and Hyrtios erecta) | Macroyclic lactone | Leukemia (Jurkat cells) |
| 10  | Streptochlorin       | Streptomyces sp. | Methyl pyridine | Leukemia (U937 cells) |

### Anticancer Compound from Marine Flora

Anticancer 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 for human treatment. 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. Mostly invertebrates that include sponges, soft corals, sea fans, sea hares, nudibranchs, bryozoans, and tunicates are proven to be the potential sources of drugs. It is now believed that microbial floras 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 medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as 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medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinally potent chemicals as polyphenols, polysaccharides and medicinal...
Marine bacteria: Produce secondary metabolites which have anticancer agents (e.g., elutherobin, discodermolide, bryostatins, and sarcodictyin) as in Table 3. Most of marine bacteria produces toxins which are useful in neurophysiological and neuropharmacological studies. 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.

Marine actinomycetes: Received very recent attention. Gutingimycin is a highly polar trisoxacarin derivative from streptomyces species, isolated from sediment of the Laguna de Terminos, Gulf of Mexico. 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. These microbes revealed to be a promising sources of anticanceragents that target proteasome function.

Thiocoraline is a novel bioactive depsipeptide isolated from Micromonaspora marina, a microorganism located in the mozambique strait that inhibits ribonucleic acid (RNA) synthesis.

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. 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.

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. More than 50% of the marine cyanobacteria are potentially exploitable for extracting bioactive substances which are effective in killing the cancer cells. Scytoxinemin 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. Largazole derived from Symploca sp. is a novel chemical scaffold with fabulous antiproliferative activity. Other compounds, aptatxin A, isolated from a strain of Lyngbya boulonii, coibamide A derived from a strain of Leptolyngbya, euracin-A, isolated from the organic extracts of curacao collections of Lyngbya majuscula.

Marine macro algae (Seaweed): Marinemacro algae many researchers have worked on the antioxidant, antitumor, and immunomodulating activities of seaweeds as edible seaweed like Pumaria palmate, the alcoholic extract of the red alga Acanthophora spicifera, the seaweeds Acanthophora spicifera, Ulva reticulate, Grazilaria fuligera, the brown seaweed Sargassum thunbergii, fucoiodan from Axophyllum nodosum, stylopoldione from Sympodium sp., kondramid-A from Chondria sp., caulerpene from Caulerpa sp., two compounds meroterpenes and usneoidone isolated from Cryptophora sp., phloroglucinol and its polymers namely eckol (a trimer), 45 phlorofucofuroeckol A (a pentamer), 45 dieckol and 8,8’-dieckol (hexamers) isolated from the brown alga eisenia bicyclis and padina 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 as source of anticancer drugs (Table 4). A sulphur containing alkaloid, 1,2-dithiolane (brugine) isolated from Bruguiera sexangula, ribose derivative of 2-Benzoxazoline isolated from Acanthus ilicifolius and tea from the mangrove plant Ceriops decandra has shown anticancer activity.

Microorganisms with Anticancer Properties

Small organic molecules derived naturally from microorganisms have provided a number of beneficial cancer chemotherapeutic drugs. 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. It is assumed that the rallied immune system, by intentionally introducing microorganisms into the oncological patient, is able to at least limit the development of cancer.

| Bacteria | Gram (+ or -) | Activity | Target organism | Disease |
|----------|---------------|----------|-----------------|---------|
| Pseudomonas bromoides | - | Anticancer | Stephatococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes | Pneumonia, osteitis, arthritis, endocarditis, localized abscesses |
| Chromobacterium marium | - | Antibacterial | Escherichia coli, Pseudomonas aeruginosa, Stephatococcus 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 aureovericillatus | + | Anticancer | Tumor cells | Tumors |
| Marinobacter diocarbonoxidatus | - | Antibacterial (iderofore) | Mycobacteria tuberculosis, Bacillus anthracis | Tuberculosis, carbuncle (anthrax-like) |

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

| Bacteria | Gram (+ or -) | Activity | Target organism | Disease |
|----------|---------------|----------|-----------------|---------|
| Pseudomonas bromoides | - | Anticancer | Stephatococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes | Pneumonia, osteitis, arthritis, endocarditis, localized abscesses |
| Chromobacterium marium | - | Antibacterial | Escherichia coli, Pseudomonas aeruginosa, Stephatococcus 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 aureovericillatus | + | Anticancer | Tumor cells | Tumors |
| Marinobacter diocarbonoxidatus | - | Antibacterial (iderofore) | Mycobacteria tuberculosis, Bacillus anthracis | Tuberculosis, carbuncle (anthrax-like) |
### Table 4. List of Anticancer Compounds Isolated from Endophytic Fungi from Mangrove Habitats

| No | Host Plant               | Fungal Endophyte | Isolated Cytotoxic Compounds                                                                 | Tested Cell Lines | Cytotoxicity          |
|----|--------------------------|------------------|------------------------------------------------------------------------------------------------|-------------------|-----------------------|
| 1  | Excoecaria agallocha     | Phomopsis sp.    | 2-(7’-hydroxyoxooctyl)-3-hydroxy-5-methoxybenzeneacetic acid ethyl ester                        | HEP2              | 25                    |
| 2  | Rhizophora mucronata     | Pestalotiopsis sp.| Cytosporones J-N                                                                                  | LS178Y            | Not Active up to 10 μg/mL |
| 3  | Rhizophora mucronata     | Pestalotiopsis sp.| Pestalosiopone A                                                                                  | NA                |                       |
| 4  | Not mentioned            | Mangrove endophytic fungus No. ZSU44                 | Secalonic acid D                                                                                  | HL60              | 0.38                  |
| 5  | Excoecaria agallocha     | Pestalotiopsis sp.| Phomopsis-H76 A                                                                                  | KB                | All the compounds are active |
| 6  | Kandelia woody tissue    | Halosorinella sp.| 1-hydroxy-3-methylanthracene-9,10-dione                                                            | KB                | 3.17                  |
| 7  | Sonneratia apetala       | Zh6-B1 (unidentified)               | 3R,5S-Sonnerlactone                                                                               | KVI/MDR           | 42.4                  |
| 8  | Xylocarpus granatum      | XGBD (unidentified)               | Merulin A                                                                                         | BT474             | 4.98                  |
| 9  | Acanthus ilicifolius     | Pestalotiopsis sp.| Penicinoline                                                                                      | HeLa              | >100                  |
| 10 | Unidentified mangrove (Taiwan Strait) | Pestalotiopsis sp.| Paeciloxocins A                                                                                  | HepG2             | 1                     |
| 11 | Excoecaria agallocha     | Penicillium expansum               | Expansols A                                                                                       | AS49              | NR                    |
| 12 | Kandelia candel          | Fusarium sp.                  | 5-O-methyl-2'-methoxy-3'-methylalpinumisoflavone                                                  | HepG2             | 11                    |
| 13 | Angicera corniculatum    | Alternaria sp. ZJ9-68            | Alperporriol K                                                                                    | MDA-MB-435        | 26.97                 |
| 14 | Rhizophora mucronata     | Irpex hynides                  | Ethy acetate extract                                                                              | HEP2              | 125                   |
| 15 | Rhizophora annamalayan   | Fusarium oxysporum             | Taxol                                                                                             | NT                | NT                    |
| 16 | Bruguiera gymnorrhiza    | Rhizidhysteran rufulum          | Rhizidchromones A                                                                                 | MCF7              | 19.3                  |

Compounds are included in the column “isolated compound/s”. NA-Not Active; NR-Not Reported; NT-Not tested
of cancer. 48 This is a method in which microbes indirectly lead to cancer regression especially 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 the destruction 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 destructed 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 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*; 58 serovar typhimurium which is obligate anaerobes and facultative anaerobes; 59 *Clostridium histolyticum*; 60 *Magnetospirillum marinum* MCI is a gram-negative coccid found in the Atlantic Ocean near Rhode Island, USA. 61

**Toxoplasma gondii:** Toxoplasma gondii is an obligatory intracellular parasite. 62 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 gondii, can be used to treat cancer. 63 Their presence in the tumor environment could have destructed 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 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*; 58 serovar typhimurium which is obligate anaerobes and facultative anaerobes; 59 *Clostridium histolyticum*; 60 *Magnetospirillum marinum* MCI is a gram-negative coccid found in the Atlantic Ocean near Rhode Island, USA. 61

**Plasmodium falciparum:** Plasmodium falciparum (Malaria) caused by *Plasmodium falciparum* 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 *Ascarhus trui* and *Sihurana tropicalis*; 68 aurein peptides from the green and golden bell frog (*Litoria aurea*) 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 phylloseaatin L1, isolated from the lemur leaf frog (*Agathelcidens 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 flasialis*).

**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 peptide neurotoxins, which are used as tools to study different ion channels, such as the Na+, K+, Ca2+, and Cl− ion channels 75 (Table 5). Chlorotoxin (CTX) is a small neurotoxin of 36 amino acids that was isolated from the venom *Leuissus quinquiesstitrus* 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, and thiolalbuminases), neurotoxins, and cytolylc peptides. 77 A short cationic peptide latarcin 2a (Ltc2a) isolated from *Lachesana taraborrivenom* have anticancer activity. 78

Venom from bees and wasps is now being studied to design and develop new therapeutic drugs from their venom. 79 Meltitin 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 leukemia, 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 lewisi* venom that has shown in vitro anticancer activity. 81

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Most snake venoms are a mixture of several proteins, peptides, toxins, enzymes and non-protein components. Bioactive peptides from snake venoms have significantly contributed to the treatment of many human diseases, and some of them may selectively target cancer cell membranes, affecting the proliferation of cancer cells.

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.

### CONCLUSION

This review aims to boost the use of natural product arising from their anticancer activities. Natural product proven to have efficacy as an 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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