UTTAR PRADESH JOURNAL OF ZOOLOGY

42(22): 57-67, 2021
ISSN: 0256-971X (P)

A REVIEW ON ANTICANCER SOURCES FROM AQUATIC ORGANISMS

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Rakpong Petkam, Khon Kaen University, Thailand.
Reviewers:
(1) Dalia Ashraf Abdel-Moneam ahmed, Cairo University, Egypt.
(2) Rusănescu Carmen Otilia, Polytechnic University of Bucharest, Romania.

Received: 13 August 2021
Accepted: 27 October 2021
Published: 02 November 2021

Review Article

ABSTRACT

Now a days the prevalence of cancer is increasing in an alarming way. There are several treatment methods for the control of cancer cells including chemotherapy, radiation, and surgery. Chemotherapy, that uses chemicals for the inhibition of cancer growth and out-turn leads to several side effects to the normal cells. Naturally derived substances are getting more attention in cancer studies as a replacement of the chemicals or enhancers of chemicals used in chemotherapy. This review intends to gives a brief account on the recently found anticancer activity of aquatic organisms or compounds.

Keywords: Cancer; cytotoxicity; aquatic microorganisms; aquatic plants; aquatic algae; fish.

1. INTRODUCTION

Cancer is a broad word that encompasses a wide range of illnesses that can affect any area of the body. One of the hallmarks of cancer is the fast emergence of aberrant cells that expand beyond their normal borders, allowing them to infiltrate neighbouring parts of the body and migrate to other organs; metastasis. Cancer metastases are the leading cause of mortality [1]. In today's world cancer is becoming a major cause of death. The cancer control using synthetic or naturally occurring agent is becoming popular now a days, but the cost and side effects of chemicals gives more attention to natural compounds in the prevention, slow down of cancer growth [2].

Many natural products that were driven from both terrestrial and aquatic life were widely used for the antitumor studies and studies that related to anticancer drug discoveries [3]. Terrestrial herbs and spices, plant, tree such as garlic, black cumin, turmeric, curcumin, *Eupatorium glutinosum*, and *Aniba panurensis* contains several bioactive compounds act as chemo-preventive, antimicrobial and antifungal agents [4-6]. To far, over 6,000 novel marine natural

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products have already been discovered, including alkaloids and peptides, steroids and lipids, phenolic and quinoid chemicals. A small number of substances have been clinically evaluated and shown to have potent anticancer, antiviral, anti-inflammatory, haemolytic, and antinociceptive properties [7,8]. Compounds that derived from marine algae, fish, tunicates and marine invertebrates such as molluscs, echinoderms have the ability to act as an anticancer or cancer preventive compounds [9-11]. The marine fatty acids have been reported with different activities such as antimalarial, antimycobacterial, antifungal and anticancer [12,14]. According to [13], different bioactive peptides from different species of ascidia, sponges, molluscs has been reported with antitumor, antitubulin, anti-neoplastic and antiproliferative activities. The cancer cell growths are inhibited through the cytotoxic effects of natural compounds by attacking the macromolecules that present on the cancer cell surface and a large number of marine derived compounds showed anticancer effects in both *in vitro* and *in vivo* studies [15-17]. This review analyses recent studies and highlights the anticancer effect of aquatic organisms, with particular emphasis on aquatic plants and algae, actinomycetes, bacteria, fungi, sponges soft corals and fishes.

2. AQUATIC MICROORGANISMS AS ANTICANCER SOURCE

Microorganisms include protozoa, bacteria, fungi and members of plant kingdom. Bacteria, the smallest group of organisms abundant in both terrestrial and aquatic environment especially the autotropic bacteria which are the primary producers in aquatic systems [18]. In 2014, study conducted by [19] reported that the compounds isolated from *Aspergillus terreus,* a marine endophytic fungus associated with the marine seaweed *Codium decorticatum* has cytotoxicity against hepatocellular cancer cell line and low toxic effect on normal cells. Similarly, the sponge associated actinomycetes, *Streptomyces sp*. with promising anticancer effect against lung cancer cell lines by the induction of apoptosis [20]. The isolated marine actinomycete strain (HP411) has been reported with anticancer activity against different cancer cell lines like liver cancer cell line, cardiac and skeletal muscle cell line and membrane of the uterus cancer cell line [21]. Most recent study found that the Sea cucumber (*Holoturia atra*) associated bacteria, *Sallinicoccus roseus* and *Sphingobium yanoikuyae* produce more anticancer potency against murine leukemia cells (P388). They also found that the *Sallinicoccus roseus* with stronger anticancer activity that were cultivated in better nutrient containing A11 bacterial medium [22].

3. AQUATIC CILIATES AS ANTICANCER SOURCE

According to [23] ciliates are free-living aquatic diverse group which act as the predators of bacteria, algae and some protists. *Tetrahymena thermophilia*, a unicellular ciliate used in the production of anticancer monoclonal antibody- rituximab. The antibody that resulted has improved antibody-dependent cell-mediated cytotoxicity [24]. Study conducted by [25] found that the secondary metabolite extracted from *Euplotes crassus* has cytotoxic effect against the different cutaneous melanoma cells. They also identified that the cell migration at the molecular level was inhibited or decreased at the molecular level by the compound Euplotin C (EC). The compound reduced the aggressiveness of melanoma cell by controlling Erk and Akt pathways.

4. AQUATIC PLANTS AND ALGAE AS ANTICANCER SOURCE

There are many aquatic plants such as Arrow Arum, *Calla Palustris*, Bur-reeds, Chara, Large Leaf Pondweed, Wild celery etc. provide many beneficial effects including food and shelter for fish, filter water, assimilate nutrients and also contains several compounds that can be used in therapeutic studies [26,27]. The simple plant-like aquatic organism without true stems, leaves or roots comes under the group algae, with importance in production of oxygen from photosynthesis waste products, nitrogen fixation, and also act as environmental quality indicators [28]. Algae contain several bioactive molecules that are derivatives of peptides, carbohydrates, and lipids which can be act as natural molecules with anticancer potential or alternative to conventional drugs [9].

Recent *in vitro* study conducted by [29] in hornwort (*Ceratophyllum demersum)* reported that the ethanolic extract of hornwort has the cytotoxicity against the human colon cancer. In the case of methanolic extract of water hyacinth reported with increased human cervical cancer cell growth inhibition [30]. Several studies identified the anticancer or cancer preventive compounds present in different algal groups [9-11]. Further studies conducted in different extractions of marine algal groups such as *Ulva lactuca, Ulva fasciata, Gracilaria edulis, Dictyota kunthii, Chondracanthus chamissoi* exhibited increased or good cytotoxicity against different cancer cells that includes human breast cancer, epithelioid carcinoma, human prostate cancer, hepatocellular carcinoma [31-

33]. In 2018, [34] found that the methanolic extract of freshwater macroalgae *Cladophora surera* inhibit breast cancer cell (MCF-7) migration and adhesion. $20\mu gmL^{-1}$ were the lowest dose that significantly reduced MCF-7 cell number to 59.86%. The fucoidan isolated from the brown seaweed inhibit the human lung cancer cell from 24.9 to 73.5% in the concentrations of 31.25 to 500µg/ml in a dose-dependent manner [35].

5. AQUATIC INVERTEBRATES AS ANTICANCER SOURCE

Animals without backbone is termed as invertebrates, are the diverse and abundant group that found in the aquatic system consist of worms, mollusks, insects etc. Most of the invertebrates present in the aquatic sediments are the indicators of aquatic ecosystem health and diversity [36]. Several studies conducted different sponges, *Dysidea avara, Spheciospongia vagabunda, Negombata magnifica, Negombata corticate* revealed that they possess high to moderate cytotoxic potency against breast cancer, myeloma, leukemia and liver cancer via increasing apoptosis activity [37,38].

Moderate inhibition activity of different sponges and soft corals towards the breast cancer (MCF-7) and lung cancer cells (HepG2) were identified by researchers in their studies. They found that *Negombata corticate* with highest activity against HepG2 with a concentration of 16.3µg/ml and *Sarcophyton glaucum* with highest activity against MCF-7 with a concentration of 18.7µg/ml [38]. Biomacromolecules present in different groups of snails were effectively used for the treatment of bladder cancer [39]. They were able to find that the Biomacromolecules (Hemocyanin) from *Helix lucorum* induce cytotoxicity and apoptosis against bladder cancer cells. The hemolymph extract of brachyuran crab (*Calappa calappa*) has been reported with increased cytotoxicity by reducing different cancer cell viability [40].

6. FISH AS ANTICANCER SOURCE

Fish form an important part of human diet due to its nutritional content such as high protein, low fat, essential amino acids, vitamins, minerals and essential fatty acids such as omega-3 fatty acids [41]. In 2020, the cell viability inhibition of Mediterranean mesopelagic fish species- lantern fish (*Myctophum punctatum*) & Mediterranean krill (*M. norvegica)* were studied and found that the lanternfish has more activity against breast cancer cell and lung cancer cells. *M. norvegica* was reported with high potency against hepatocyte carcinoma [42]. Researchers reported that the acetic acid extract of skin, liver, intestine and muscle of puffer fish (*Arothron stellatus)* possessed anticancer activity with percentage of cell inhibition 15%, 34%, 7% and 5% respectively [43]. The lipid extract of *Labeo rohita* inhibit prostate cancer cells (PC3) via changing the morphology, decrease the number of cells and induce apoptosis in cancer cell lines. Different doses of total fish lipids (10, 25 and 50 mg/ml) caused the reduction of the PC3 cells (84.81%, 44.57%, and 27.04% respectively) [44]. The pituitary adenylate cyclase-activating peptide from North African catfish has been identified as a regulatory neuropeptide not only act as antibacterial agent but also act as an antiproliferative agent that control the growth of human non-small cell lung cancer [45].

Study conducted by [46] investigated the anticancer activity of fractionated eel protein hydrolysate (EPH) against breast cancer cell lines and identified that decrease in the molecular weight of EPH increases the cancer cell growth inhibition. Polyunsaturated fatty acid extracts of sardine fish and crude epidermal mucus of mullet fish has the ability to control the growth of cancer cells which includes breast cancer, prostate cancer and laryngeal cancer cell lines respectively [47,48]. According to the American Institute of Cancer Research, increased consumption of fish reduced the risk of liver, colon and breast cancer and the meta-analysis of fish consumption with lung cancer revealed its protective aspect [49,50]. Another finding that related to the anticancer activity of fish is that the by-products from fishes like salmon, barramundi, wild caught flathead and silver warehou contained the anticarcinogenic peptides, which opened the entry of the products into pharmaceutical industry [51]. Most recent study conducted in 2021 revealed that the use of fish oil in combination with selenium increase the efficacy of Avastin, which used for the treatment of different type of cancer. And this particular study found that the combinations enhance the therapeutic activity of Avastin through targeting multiple pathways and act against triple negative breast cancer (TNBC) in dose dependent manner [52].

7. CONCLUSION

Recent years, the attention towards the natural products that derived from aquatic system were increasing for different therapeutic activity, especially for the anticancer activities. Most of the recent studies conducted in different aquatic organisms such as aquatic microorganisms or associated ones, plants, seaweeds, algae, sponges, corals, and different fish species revealed that they possessed cytotoxic potency against several types of cancer cell lines. From different studies it can be concluded that these

organisms are real boon for the therapeutic research, which are highly effective towards the breast cancer, lung cancer, cervical cancer, prostate cancer and leukemia. Further intensive investigations are needed to establish a clear idea about the functioning of aquatic organisms against different cancer cells. The summarized data of different aquatic organisms and their compound effects upon tumor growth, cancer cell viability and induction of apoptosis are presented in the Table 1.

Table 1. Effect of different aquatic sources on different cancer cell lines

Aquatic source organisms	Species	Extract/ Compound	Cancer	Cell line used	Effect of extract/ compound	Inhibitory concentration/ IC_{50}	Reference
Sea cucumber (*Holoturia atra*) associated bacteria	*Sallinicoccus roseus* (HPP.4A) *Sphingobium yanoikuyae* (HPP.T13)	Extracted using 1-butanol with maceration method	Murine leukemia cell	P388	Produce more anticancer potency	-	[22]
Sponge associated endosymbiotic actinomycete	*Streptomyces sp* (MCCB 267)	Crude extract	Non- Small Cell Lung Cancer	NCI-H460	Induction of apoptotic pathways leading to cell death	IC_{50} = 2.3µg/ mL (NCI-H460)	[20]
Marine Actinomycete Strain	*Streptomyces variabilis* (HP411)	Active strains	Liver cancer cell line Cardiac and skeletal muscle cell line Cervical carcinoma	Hep-G2 RD cells FL	Changed shape and lost cell contacts, cells lost their surface morphology	IC_{50}=13.7 µg/ml (Hep-G2) IC_{50}=40µg/ml (skeletal muscle) IC_{50}=4.41µg/ml (cardiac RD) IC_{50}=12.6 µg/ml (FL)	[21]
Seaweed endophytic fungus	*Aspergillus terreus*	Active fraction of *Aspergillus terreus* (F7 and F8)	Hepato-cellular carcinoma	HepG2	Potential cytotoxicity	GI_{50} of F8 on HepG2 cancer cell line was <10	[19]
Marine Ciliate	*Euplotes crassus*	Euplotin C	Human Melanoma Cells	A375, 501Mel, MeWo.	Cytotoxic potency, proapoptotic activity and a decrease in melanoma cell migration	IC_{50} =3.53 ± 0.19µM (A375) IC_{50} =2.68 ± 0.29µM (501Mel) IC_{50} = 3.56 ± 0.38 µM (MeWo)	[25]
Freshwater ciliate	*Tetrahymena thermophila*	Monoclonal antibody production	Mammalian cell lines	-	Increased cytotoxicity	-	[24]
Hornwort (Aquatic plant)	*Ceratophyllum demersum*	Ethanol extract	Human colon malignant growth cell line	HT-29	Cytotoxicity	800µg/ml of ethanol extract - growth inhibition (Cell viability: 46.18±0.61)	[29]

Water hyacinth (Mart)	*Eichhornia crassipes*	Methanol extract	Human cervical cancer cell line	HeLa	Increases the cell growth inhibition	IC_{50}=32.33µg/mL (HeLa)	[30]
Marine Macroalgae	*Ulva lactuca* *Ulva fasciata*	Seaweed chloroform extract	Human breast cancer Epithelioid Carcinoma Human prostate cancer Hepatocellular carcinoma	MCF-7 Hela cell lines PC3 HepG2	Cytotoxic activity	*U. lactuca* extract IC_{50}=10.83±1.0, (MCF-7) IC_{50}=12.43±1.3 µg/ml (Hela) *U. fasciata* extract IC_{50}=12.99±1.2 µg/ml (PC3) IC_{50}=16.75±1.5 µg/ml (HepG2)	[31]
Marine red algae	*Gracilaria edulis*	Methanol extract	Breast cancer cell line	MDA-MB231	Good toxicity over cancer cell line	A maximum of 94.06% cell viability for 20µg of crude methanolic extract	[32]
Brown seaweed (Algae) Red seaweed (Algae)	*Dictyota kunthii,* *Chondracanthus chamissoi.*	Sequential extract	Human colorectal adenocarcinoma Human breast adenocarcinoma	HT-29, MCF-7	Cytotoxic activity	*D. kunthii* 23.81 ± 1.98% cellular viability *C. chamissoi* 29.28 ± 2.60% cellular viability	[33]
Freshwater macroalga	*Cladophora surera*	Algal extract (methanol)	Human breast cancer	MCF-7 cells	Inhibit cell migration and adhesion	20 μgmL^{-1} lowest dose that significantly reduced cell number to 59.86%.	[34]
Brown seaweed	*Turbinaria conoides*	Fucoidan	Human lung cancer	A549	Moderate cytotoxicity	Anticancer activity from 24.9 to 73.5% in the concentrations of 31.25 to 500 µg/ml in a dose-dependent manner	[35]
Purple sponge	*Dysidea avara*	Ethanolic extract	Myeloma Human breast cancer Chronic	H929 MCF-7 K562	Cytotoxic effect, High capacity of inducing apoptosis	IC_{50}=2.91 ± 0.51µg/mL (H929) IC_{50}=11.51 ± 1.94µg/mL (MCF7)	[37]

			myelogenous leukemia				
			Human cervical carcinoma	HeLa		IC_{50}= 7.17 ± 1.30µg/mL (K562)	
			Human colon cancer cell line	HCT116		IC_{50}=5.11 ± 0.72µg/mL (HeLa)	
						IC_{50}= 17.54 ± 2.28µg/mL (HCT116)	
Sponge	*Spheciospongia vagabunda,*	Extract	Breast cancer cell line	MCF-7	Cytotoxicity	*N. corticate* IC_{50}= 16.3± 0.24µg/ml, 24.7±0.67µg/ml on HepG2, MCF-7 respectively	[38]
	Negombata magnifica,		Liver cancer cell line	HepG2			
	Negombata corticate						
Soft corals	*Sarcophyton auritum*	Extract				*S. vagabunda* IC_{50}=28.1±0.68 µg/ml, 19.7±0.3µg/ml on HepG2, MCF-7 respectively	
	Sarcophyton glaucum					*S. glaucum* IC_{50}=19.3±0.18 µg/ml, 18.7±0.51µg/ml on HepG2, MCF-7 respectively	
						S. auritum IC_{50}=18.2±0.49 µg/ml, 21.1±0.72µg/ml on HepG2, MCF-7 respectively	
						N. magnifica IC_{50}=19.2±0.37 µg/ml, 25.8±0.9µg/ml on HepG2, MCF-7 respectively	
Mollusca	*Helix lucorum (HlH)*	Biomacromolecules (Hemocyanin)	Bladder cancer cell	CAL-29	Induction of apoptosis, inhibition of cell viability dose- and	72 hours of incubation, the respiratory activity of the cells reduced to	[39]
	Rapana venosa (RvH)						

	Megatura crenulata (KLH)				time-dependent	67% with 300 µg/mL of HlH and to 41% with 150 µg/mL of RvH	
Brachyuran crab	*Calappa calappa*	Hemolymph	Breast cancer cell line Liver cancer cell line Adeno-carcinomic human alveolar basal epithelial cells Human colorectal adenocarcinoma Rhabdomyosarcoma cell lines	MCF-7 HepG2 A549 HT-29	Cytotoxicity, reduced the cell viability	IC_{50}= 75 µg mL^{-1} (MCF-7) IC_{50}= 100µg mL^{-1}(HepG2) IC_{50}= 95µg mL^{-1}(A549) IC_{50}= 95µg mL^{-1}(HT-29) IC_{50}= 100µg mL^{1}(Rhabdomyosarcoma)	[40]
Pufferfish	*Arothron stellatus*	Acetic acid extract	Human lung carcinoma	A549	Cell inhibition	Cell inhibition percentage at 10µl of skin, liver, muscle and intestine extract = 15%, 34%, 5% and 7% respectively	[43]
Lanternfish Mediterranean krill	*Myctophum punctatum* *Meganyctiphanes norvegica.*	Chemical extraction	Human lung carcinoma Breast adenocarcinoma Hepatocyte carcinoma	A549 MCF7 HepG2	Cell viability inhibition	*M. punctatum* IC_{50}= 13.77–23.26µg/mL (A549) IC_{50}= 25.34–29.62µg/mL (MCF-7) *M. norvegica* IC_{50} between 3.81 and 7.51µg/mL for HepG2	[42]
Freshwater fish	*Labeo rohita*	Lipid	Prostate cancer	PC3	Change morphology, decrease cell number, induce apoptosis	10mg/ml of total fish lipid caused reduction of 84.81% of PC3 25 mg/ml of	[44]

						total fish lipid caused reduction of 44.57% of PC3 50 mg/ml of total fish lipid caused reduction of 27.04% of PC3	
North African catfish	*Clarias gariepinus*	Pituitary adenylate cyclase-activating polypeptide (PACAP)	Human non-small cell lung cancer cell line	H460	Affects the proliferation of cancer cell	IC_{50}=13.17 µM	[45]
Asian swamp eels	*Monopterus sp*	Fractionated eel protein hydrolysate (EPH)	Breast cancer	MCF-7 cell	Cancer cell inhibition increases with decrease in molecular weight	IC_{50} value of EPH= 6.50 µg/ml (For different fractions of EPH;10 kDa, 5 kDa and 3 kDa IC_{50}=21.50µg/ml,16.84µg/ml, 11.08 µg/ml respectively)	[46]
Marine fishes (Sardines)	*Sardinella longiceps* *Sardinella fimbriata*	Polyunsaturated fatty acid extract	Breast cancer Prostate cancer	MCF-7 DU-145	cytotoxic effects	*S. longiceps* IC_{50}=81.17µg/ml (MCF-7) IC_{50}=53.07µg/ml (DU-145) *S. fimbriata* IC_{50}=180.01µg/ml (MCF-7) IC_{50}=67.64µg/ml (DU-145)	[47]
Mullet fish	*Mugil cephalus*	Crude epidermal mucus	Laryngeal cancer cell lines	-	anticancer activity	1000µg/ml with significant lytic activity. IC_{50}=7.8125µg/ml	[48]

ACKNOWLEDGMENT

The authors wish to acknowledge all the researchers for their contribution in the field of importance of aquatic organisms in therapeutics and making the data available printed and online.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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