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Promising Updates in Biodiversity as Anti-cancer drugs: A short review

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Abstract

Owing to the modern life style cancer is a major disease of the modern society. Though lot therapies are there to control cancer, drug based control is considered as a major control measure. The biochemicals isolated from the natural organisms are of immense value as these products have fewer side effects. The action of the biochemical is majorly by intercalation or the groove binding to DNA and regulating the uncontrolled proliferation of tumor by chromosomal breakage or cytolysis. The phyto-chemicals are promising candidates a have diverse type of secondary metabolites, some of which are proved to be efficient drugs in cancer therapy. Another source of cancer drugs are the marine biodiversity, ranging from bacteria to Mollusca. These organisms also develop secondary metabolites for self defense and predation, which is gaining wide attention presently. The current review seeks the advancements of cancer therapy in this context.

Keywords:

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1. Introduction

In human body billions of cells are present which perform different functions .The functioning of cells are complicated process and are under incredible phenomenal control. In cancer, cells lose the ability to follow the normal control that the body exerts on it [1, 2]. Slight deviation in a particular cell function that escapes the normal control mechanism continues to grow abruptly and cause tumor [3,4]. Significant advances in science and technology has changed the scenario of understanding and treatment of cancer more effective in this century, even though cancer has been known since antiquity [5, 6]. Theses advancements led to the major landmark in timely and

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accurate diagnosis, surgery and radiation therapy [6,7]. The discovery of radiation therapy has become a remarkable method in cancer treatment. Through advancement in cell biology, genetics and biotechnology researchers gained knowledge regarding the changes within cells that paved way for converting normal cells to malignant cells. The actual gains delivered from conceptual gains in the practice of cancer diagnosis and treatment, led to the most promising area of tailored cancer therapy in which biological anomalies unique to the diseases.

In chemotherapy the cancer cells are destroyed using bystander mediated killing [8]. In a tumor, the cell population will be of heterogeneous nature [9]. They possess malignant as well as non-malignant cells [10]. The nonmalignant cells contain immune cells, endothelial cells and fibroblast that interact with themselves as well as malignant cells [11]. Tumor associated macrophages are the most abundant immune cells present in tumors [12]. Tumor associated macrophages can be targeted with the help of protein [13] and approximately more than 60% of tumor mass can be reduced thereby increasing therapeutic index. In this report, the characterization and the biological properties of a group of bioactive potential compounds which are used for anticancer treatment have been furnished.

Anticancer drugs

Anticancer drugs or the antineoplastic drugs are used in association with surgery, radiotherapy and immunotherapy for the treatment of cancer. These drugs have enough potential to target the metastatic fast dividing oncogenic cells [14]. Based on the mode of action or origin, they are classified as alkylating agents, antimetabolites, plant or microbe derived biodiversity products and hormones [15]. Alkyl sulfonates, triazene, nitrosoureas, platinum Coordination complexes (cisplatin, carboplatin, oxaliplatin), Methyl hydrazines, Nitrogen mustards, melphalan, cyclophosphamide and ifosfamid and some examples of the alkylating agents. While, purine antagonists, folate antagonists (methotrexate) pyrimidine antagonists (5-fluorouracil, cytarabibe) are classified as antimetabolites. There are also compounds which do not be included in any of the above category but are potential anticancerous drugs.

DNA Targeting

Molecular pathways of compound drug effects and specific compound–substrate interaction is very crucial in the development of new drugs and also for existing drugs. Molecular studies had led to the identification of promising and efficient antitumor strategies [16]. Versatile therapeutic results were achieved by the gene expression alternations through the small DNA binding particles. The product targeting the DNA can modify gene expression leading to alterations in the regulation of cell growth. Systems biology approach suites to capture the complexity of drug activities in cells [17,18, 19]. Prediction of mode of drug action has been attempted by using gene expression profiles. The steps involved in this are the treatment using appropriate drug, identifying and comparing the side effects, literature text mining and applying chemo-informatics tools

Gene Signature

Gene signature is the most promising approach for discovering the connections among drug pathways [20, 21], disease or compounds [22,23]. Gene signature is based on the subset of genes whose differential expression can be utilized as a marker of the given pathway/disease/compound using a large collection of transcriptional responses. These are followed by compound treatment like connectivity map.

Drug-DNA interaction

DNA is the molecular target for many drugs in cancer treatment and is considered as a nonspecific target to many cytotoxic agents [24]. Anti-neoplastic agents inhibit DNA synthesis and makes irreversible or reversible damage to DNA. Anti-cancer treatment basically depends on small molecules [24,25] which are protein in nature that can target receptors. DNA drugs generally works by two methods, neither by intercalation nor by groove binding [25].

Intercalating drugs enter and intercalate with DNA molecules of the cancerous cells and interfere in the late S or G2 phase [26,27]. This can cause block in the DNA replication and cell cycle, hindering the cell from replication. Intercalating agents decrease the DNA helical twist and

lengthening of the DNA. Main intercalaters are compounds with bi or tri cyclic ring structure [28]. Significant amount of free energy is needed for the intercalation of drugs in DNA (approximately 4 kilocal Mol) [26,27,28,29]. The Intercalated compound interfere with the topo-isomers, bind to nuclear DNA leading to DNA breakage, chromosome damage and sister chromatid exchange in the cells. DNA intercalation induces structural changes in DNA leading to intrusion in the recognition and function of DNA associated proteins such as transcription factors, DNA repair systems, polymerases and topoisomerases. This can lead to cytotoxicity and the damage to cancer cell.

DNA groove binding molecules are characterized by several aromatic rings that are connected and allowing freedom of movement and torsion [26, 29]. Groove binders are crescent shaped molecules that bind to the minor groove of DNA. It includes standard lock and key models for ligand macromolecular binding. They are stabilized by intermolecular interaction. Their association constants are higher as they do not require free energy for binding site [30]. Groove binders have been clinically used as anticancer and antibacterial agents. The DNA groove binders will not alter the structure as well as there is no change in free energy structure [27,28,29]. The most promising characteristics of DNA binding compound is that they bind to AT rich area due to the powerful hydrophobic interaction between aromatic ring the compound and second C atom of adenine. Groove Binding drugs are very promising because of their possible effect on pronounced affinity, gene expression and selective binding.

Plant derived anticancer compounds

It is well known that the treatment of cancer is highly complicated, as some of the medicines target not only cancer cells but normal cells also. This leads to the side effects associated with the drug usage [31]. Anticancer agents are generally toxic and cause various side effects that include hair loss, mouth sores, bone marrow toxicity, anemia, cardiac anomalies, severe nausea, vomiting and in rare cases permanent infertility. In this context, derivatives from medicinal plants have gained immense significance in the treatment of cancer (www.cancer-concerns.com/chemsideffects.htm). According to WHO, 80% of world's population rely on plant derived medicines for healthcare. About 60% of the drugs approved for cancer treatment are of natural origin. Fruits and vegetables contribute main sources of β carotene, α-tocopherol, fibers, vitamins C, B, E that have cancer healing capacity. Plant derived agents are successfully utilized in cancer treatment [32]. Herbal drug formulations for cancer treatment and the natural sources of potential therapeutic effects of these products increase the life expectancy.

Antioxidants play an important role in reducing the development of tumor by regression of premalignant lesions and inhibit their development into cancer [33]. Studies have indicated that some antioxidants like β carotene benefit the treatment conditions of oral leukoplakia. The major antioxidant phyto-compounds are isoflavones, flavones, anthocyanins, flavonoids, lignans, coumarins, isocatechins and catechins [32].

Some examples include vinblastine and vincristine (*Catharanthus roseus*), epipodophyllotoxin, an isomer of podophyllotoxin (*Podophyllum peltatum* roots), paclitaxel (*Taxus baccata*, *T. brevifolia*, *T. canadensis*), camptothecin (*Camptotheca acuminata*), homoharringtonine (*Cephalotaxus harringtonia* var. *drupacea*), elliptinium (*Bleekeria vitensis*), flavopiridol (*Dysoxylum binectariferum*), and ipomeanol (*Ipomoea batatas*). The two plant derived natural products, paclitaxel and camptothecin were estimated to account for nearly one third of the global anticancer market, respectively [34]. Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation.

Marine anticancer compounds

Oceans constitute 70% of the world's surface and majority of species diversity is in the ocean fringe. Total marine species may approach about 1 to 2 million. Intense efforts have been conducted over the past decade to explore the bio-chemical diversity offered by marine life for anti-cancer treatment (http://shodhganga.inflibnet.ac.in/bitstream/10603/28190/11/11_chapter%207.pdf). The intense

concentration of species co-existing in the marine habitat makes them highly complex and competitive. Motile and non-motile marine species are in constant battle for sufficient nutrient, light, temperature, water current etc. This intense competition led a high percentage of species to evolve chemical means to defend against predation, overgrowth by competing species or to subdue motile prey species for ingestion. The major biochemical used in defense are terpenoids, polypeptides, peptides, alkaloids, shikimic acid derivatives, sugar, steroids and a multitude of mixed biogenesis metabolites. Clinical trials for anti-cancer compounds derived from diverse marine life is increased today. It is considered that the evolution in the field of marine natural product drug discovery will be successful in identifying future anticancer drugs [35].

Several types of unique toxins have been identified by marine biologicals and naturalists. Early investigations gave rise to broad surveys of marine life for novel natural products with useful biological properties. They prioritize description of structural chemistry rather than drug discovery. Some of the microbial processes are also utilized in the generation of bioactive and potentially useful marine products. Marine microalgae, cyanobacteria and heterophobic bacteria which are seen in association with invertebrates produce bioactive and useful constituents. Sea weeds are also used as dietary fibers function as antimutagenic, anticoagulant, antioxidant and antitumorous agents [36]. Sarcodictin, bryostatins, discodermolide and elutherobin are some of the agents isolated from marine bacteria against cancer. Streptomycet species isolated from the sediments showed the presence of Guntingimycin (a trioxacarcin derivative) which is a potent anti-cancerous drug [37].

Molluscan Dipeptide

From the molluscan species, *Elysia rubefescens* a dipeptide called Kahalalide F (KF) is isolated. This peptide is synthesized by microbes associated with the animals. KF blocks cell cycle in G1 phase in a P 53 independent manner and induces cytotoxicity [38]. The activity of this compound is demonstrated in breast, colon and prostrate cancer lines. It is also reported that a metabolite macrolactin A present in the *Noctiluca scintillans*, inhibits B16-F10 murine melanoma cancercells, protects T lymphocytes against human immunodeficiency virus replication as well as mammalian herpes simplex virus [36,37,38]. Marine actinomycetes (Family Micromonosporacea) are very promising as it is found to be a potent source of anticancer agents which target proteasome function. Thiocoraline is a bioactive anti-cancerous actinomycet derived dipeptide inhibits RNA synthesis [39].

Bacterial anticancer compounds

It is well known that the probiotic bacteria such as *Lactobacillus* and *Bifidobacteria* control the pathogenic microbes. They produce antibacterial protein called bacteriocin and anticancer substances [40]. The effect of this help in reducing colon cancer by stimulating and modulating the mucosal immune system .The effect of pro inflammatory cytokines block NFKB pathways increasing production of cytokines such as IL-10 and host defense peptide such as Betadefensin enhancing IgA defenses. This defenses dendritic cell maturation as well as modulation of cell proliferation and apoptosis through cell responses to short chain fatty acids. They are gram-positive, spore-forming soil organisms that form a true mycelium. Thiocoraline is cytotoxic against melanoma, colon and lung cancer. It exerts preferential anti-proliferative effects on colon cancer cells with defective P 53 system [41].

Cancer and challenges

One of the most fundamental advantages in the pathway of research on the treatment of cancer is the outcome from patient affected by the disease. Development of more effective and less toxic treatment has to be researched. Compared to surgery, chemotherapy and radiation therapy, the implementation of targeted therapy, immunotherapy and cancer vaccines need to be developed further [42]. Further studies has to be conducted to concentrate on the better management of toxic effects of the treatment wherein the patients ability to receive effective treatment is prioritized.

Research on cancer therapy has revealed that even within a given cancer, there are differences in the behavioral aspects as well as how it responds to treatment. Scientists have

identified various epigenetic, genetic and molecular changes that promote the development of tumor. Tumors have the ability to manipulate the immune system and turn down the immune responses and reprogram the normal cells and promote them to grow and spread. Researchers also worked on the ways how the tumor thrive and survive in the body. This understanding created opportunities to develop target therapies. Growth and development of cancer is reduced by targeting specific changes in protein. The advantage over the existing cancer therapies like surgery, chemotherapy and radiotherapy is the emergence of target therapy and immunotherapy that harness the power of immune system to fight cancer.

Researchers identify genomic similarities between endometric and other type of cancers (breast,ovarian and colorectal) in which similar molecular changes are shared. Target therapies that target specific molecular changes may act against the existing cancer but also against tumors from other sites that specifies same alterations. In conclusion many research advancements in the field of cancer treatment has been developed. Numerous challenges remain which affect the goal of providing required outcome for patients.

1. Major challenge is to eradicate the lethal effects of radiation and chemotherapy drugs on the surrounding normal tissues. Need to develop drugs which are more effective in treatment as well as alleviate the side effects of all form of cancer treatment.
2. Research is required to overcome the drug resistance acquired over a period of time with respect to traditional chemotherapy drugs.
3. In target therapy, some of the drugs responses that lead to autoimmune damage to normal tissue.
5. Genomic characterization of tumors paved way for cancer treatment identifying various molecular aspects of the tumor as it may vary in a single tumor that is present in an individual. This leads to a condition wherein the drug effective in one part of the tumor may not be effective in other part.

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