Use of natural products and their derivative in cancer research for the discovery of safer treatments

Abstract

Cancer stands as the second leading cause of death after cardiovascular disease worldwide. Many new techniques and procedures have been made in the treatment and control of cancer progression, but many deficiencies and challenges are still being faced. Chemotherapy is normally used for cancer treatment all over the world but it has many undesired side effects like fatigue, hair loss, frequent infection, and anemia. Cancer cells lose some regulatory functions resulting in continued division, which makes cancer cells susceptible to chemotherapeutic drugs. New biomedical tools for safer treatments for this disease are badly needed to improve cancer incidence in the human population. Systemic drug discovery launched a big collection of useful chemotherapeutic agents but toxicities like myotoxicity cardiotoxicity, renal toxicity, pulmonary toxicity, etc. are problematic issues. Natural therapies, derived from plants can decrease such side effects. With the help of animal models, many natural products are being explored and used to treat cancer all over the world. Animal models of cancer can mimic the disease in terms of morphology, biochemistry, and genetics could be helpful to identify the mechanism by which this disease develops in humans. Natural compounds have gained much attention as many compounds have shown very promising anti-cancer properties in vitro, but have yet to be evaluated in humans. In this review, we compile some natural anticancer drugs which are in clinical trials.

Keywords Anticancer drugs, cancer, Secondary metabolites, plants, microorganisms, animal models

Introduction

In cancer, the natural cell starts deforming due to genetic mutations in DNA. This abnormal cell replicates irregularly by asexual reproduction without responding to signals that regulate cell growth around them and obtain invasion characteristics. Cancer is an important health problem in developing and developed countries [1]. Death due to cancer is on increase all over the world, with the prediction that 13.1 million deaths will occur because of cancer all over the world by 2030 [2]. Among all cancer types, colorectal breast and lung cancers make up most of the cancer incidence all over the world [3-5]. Cancer is mainly treated by surgery, chemotherapy, radiotherapy, cancer-targeted therapy, and/or immunization therapy among which chemotherapy is the principal therapeutic method employed to treat cancer [6]. In addition, some new natural compounds are used as anti-cancer therapeutics, as drug delivery elements, or as chemoprotective agents. To improve cancer incidence in the human population, some new biomedical tools for preventive and therapeutic schemes which are safer and cost-effective are badly needed [7]. In chemotherapy, a high percentage of healthy cells get damaged. The most difficult thing in cancer dealing is to destroy tumor cells, without touching normal tissue parts [8-9]. Cancer treatment needs a lot of improvement in terms of drugs used for chemotherapy with fewer side effects. Man-made chemotherapy drugs are highly toxic with adverse effects like weight loss and lack of appetite. According to Demain & Vaishnav [10], anticancer remedies present in natural products have potential. Natural products with anticancer activity are reported in plants, microorganisms, and marine life which are almost sixty percent effective in cancer

treatment [11] The anticancer mechanism of natural compounds works by regulating the immune system. The compounds have the ability to induce apoptosis, autophagy and can also induce the proliferation of cells to inhibit tumor spread [12,13].

Plant-derived drugs used in cancer treatment

Natural products present in medicinal plants can play a significant role in cancer treatment due presence of effective chemical compounds with anti-cancer properties [14,15]. These products have potentially provided new anticancer agents with unexpected mechanisms of action [16] Recently, most developing countries utilize herbal medicine in the form of plant extracts to treat various ailments [17].

Many drugs derived from plants have shown good results against cancer and are now in clinical trials. Plant-derived drugs are natural and are safe for oral use with dietary intake in patients [18]. As these compounds are derived from natural products, they are well tolerated and non-toxic to normal human cells [19]. Plant-derived drugs can lead to clinical trials if they are non-toxic to normal cell lines and show cytotoxicity in cancer cell lines. Plant-derived drugs are of four types methyltransferase inhibitors, DNA damage preventive drugs, antioxidants, histone deacetylases inhibitors, and mitotic disruptors [18]. Some plant-derived histone deacetylases inhibitors are sulforaphane, isothiocyanates, isoflavones, and pomiferin. These compounds can inhibit the activity of carcinogenic proteins like sulforaphane can inhibit breast cancer proliferation. Plant-based histone deacetylases inhibitors can enhance chemotherapeutic sensitivity in human cancers [18, 20,21]. Vinca alkaloids, vincristine, vinblastine, vinorelbine, vindesine, and vinflunine are some drugs originally derived for plants' anti-mitotic and anti-microtubule properties. These compounds can be binding to β-tubulin to inhibit the dynamics of microtubules. Plant-derived Taxanes also act as microtubule disruptors. These natural products

can inhibit cell cycle phase transitions from metaphase to anaphase by triggering cell cycle arrest and apoptosis. Paclitaxel is one of the first natural drugs which was reported to reduce cancer cell replication [22-24]. Many plants based anticancer compounds have killing activity specific to cancer cells only without showing any effect on normal lymphocytes and fibroblasts which makes them more desirable therapeutic agents as compared to chemically derived compounds which cause toxic complications in cancer treatment [25].

An estimation in 2007 done by World Health Organization showed that the plant-derived drugs trade was worth US$100 billion which is believed to reach US$5 trillion by 2050 [26]. Medicinal plants are in high demand in cancer research due to their non-toxic effects on normal cells and cytotoxic effects on cancer cells. Numerous species of plants are being investigated in developing countries for their herbal therapies against cancer [27-30]. Medicinal plants are in demand all over the world and almost all parts including the stem, leaf, root, and bark of plants are being explored for cancer treatment. In many countries, medicinal plants are being cultivated due to high demands for alternative natural drugs [31].

Many anticancer drugs sequestered from plant materials are tested on various cancer cell lines and experimental animals after purification and then sent to clinical trials. Currently, there has been a dynamic increase in the number of newly discovered natural compounds. In 2007, about fifty thousand such substances were known, whereas, in 2015, the number of the newly discovered molecules increased up to 350K. In addition, there are 195,000 pharmacologically active compounds for which the interactions are quantitatively known [32]. Plants that have been used in traditional medicine for centuries have found application as sources of materials that possess high biological activity [33]. One approach is to obtain these substances through extractions from plant materials. Another approach is to use biotechnological tools to produce

plant-derived anticancer compounds. The substances of natural origin (e.g., from plants and aquatic animals) that exhibit antitumor properties belong to various groups of compounds, such as alkaloids, diterpenes, diterpenoquinone, purine-based compounds, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, macrocyclic polyethers, etc. Sometimes, the cost of extraction of these substances from natural materials is much lower than the cost of their chemical synthesis [34].

Currently, almost a thousand plants species have been identified with noteworthy anticancer potential [35-36]. The isolation of the vinca alkaloids, vinblastine [37] from the Madagascar periwinkle, and Catharanthus roseus G. Don. (Apocynaceae) is one of the main causes of anticancer medicine. Besides this vincristine and other cancer chemotherapeutic drugs are used for the treatment of a range of cancers such as leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma [38]. The innovation of paclitaxel [39] from the bark of the Pacific Yew, Taxus brevifolia Nutt. (Taxaceae), is another major success story in natural product drug discovery. Utilization of various parts of Taxus brevifolia from which paclitaxel was discovered and other Taxus species (e.g., Taxus Canadensis Marshall and Taxus baccata L.) by several Native American Tribes kindle the idea of indigenous knowledge-based medicinal plants [38]. Another potent plant-acquired active compound, Homoharringtonine was extracted from the Chinese tree Cephalotaxus Harrington var. drupacea (Sieb and Zucc.) (Cephalotaxaceae) and has been used successfully for a long time in China in a racemic mixture with harringtonine for the treatment of acute myelogenous leukemia. Elliptinium, a derivative of ellipticine, isolated from a Fijian medicinal plant Bleekeria vitensis A. C. Sm., is shipped to France for the treatment of breast cancer [38]. These events represent

only the surface of the success story of plant-based anticancer drug discovery with a promise to find more in the near future.

Marine-derived drug used in cancer treatment

Nowadays marine animals are being explored for anticancer therapeutics and many different types of chemicals have been isolated and used for cancer therapy [40] Marine sponges, algae, or corals are found to be rich in secondary metabolites with unique anticancer properties [41]. Many marine-based compounds have biochemical versatility for the development of many kinds of drugs. Some compounds are found active in cell growth suppression for many kinds of cancer cell types. These molecules have the potential to inhibit cell proliferation, induce apoptosis, and inhibition the metastatic potential of cancer cells. Although a lot of research is going on anticancer drugs from marine toxicity studies of marine-based drugs on in normal cells are lacking in the literature and need to be addressed. Till now almost twenty thousand novel compounds with medicinal value have been discovered from marine sources . Recently many marine secondary metabolites are being considered as drug candidates which are preclinical or early clinical trials. Many are already approved and available in the market [42].

The food and Drug Administration (FDA), has approved many marine drugs till now which are in clinical trials now. [43]. The Brentuximab vedotin 63 (Adcetris™) is approved for anaplastic cell lymphoma. Adcetris, Cytarabine, Eribulin mesylate (Halaven ®), Trabectedin are among the leading drug used for cancer treatment [44-46]. Some of the marine anticancer drugs have the potential for intractable cancer variants [47]. Some marine anticancer drugs are in phase III clinical trials which include depatuxizumab mafodotin, enfortumab vedotin lurbinectedin (Zepsyre®), marizomib, plinabulin polatuzumab vedotin, enzastaurin and lestaurtinib. Also, drugs in phase II clinical trials include GSK2857916, aplidine, plitidepsin (Aplidin®)

ladiratuzumab vedotin, PM060184 tisotumab vedotin, indusatumab vedotin, glembatumumab vedotin. The drug in phase I clinical trial includes midostaurin (Rydapt®).

Microorganisms as sources of drug used in cancer treatment

Microorganisms are a rich source of natural products that can be used for drug discovery. Isolation of diverse natural products from a microorganism mainly depends on the type of species and this method is cost-efficient in comparison to the chemical synthesis process [48]. Several microorganisms are continuously being screened for anticancer drugs all over the world [48-51]. Many bacteria, for example, *Clostridium, Bifidobacterium, Listeria*, *Escherichia coli*, and *Salmonella* have intrinsic cancer-targeting activities. Streptococcal cells were used by scientists to cure patients with inoperable cancers. Current progress in immunology and biotechnology has encouraged researchers to use bacterial in clinical applications for cancer researchers [51]. Some anticancer drugs isolated from bacteria are actinomycin D, bleomycin, doxorubicin, mitomycin C. and diphtheria toxin [52]. Nearly 53% of the FDA-approved drugs produced from natural products are isolated from microorganisms [53]. Rapamycin present in from *Streptomyces rapamycinicus* inhibits proliferation, triggering apoptosis, and inhibiting angiogenesis in a cancer cell [54,55]. Fungal furan steroid isolated from a Wortmannin has effective anticancer activity by selective inhibition of phosphoinositide 3-kinases enzymes in breast cancer [56-58]. Geldanamycin derived from Streptomyces hygroscopicus is an anticancer agent against myeloma, breast, and prostate cancer [59]. Epothilone is an anticancer agent produced from mycobacterium *Sorangium cellulosum.*

Role of animal models and cell lines in cancer drug discovery

Many experiments have been performed to mimic features of cancer cells in humans either by generating tumors in living organisms or by studying cancer in cultured cells. The importance of in vivo and in vitro models for cancer research lies in the possibility of providing an improved understanding of cancer biology and cancer treatment. Anticancer properties of herbal medicines can also be tested in animals or cell lines. Human cancer cell lines being used as a valuable tool in cancer research for decades [60-61]. These studies are being promoted all over the world to understand the genetic and epigenetic mechanisms of cancer. Cell lines are used as a basic tool to check the efficiency of herbal medicine in terms of cytotoxicity[60]. Different kinds of animal models are also being used for Vivo experiments to test the anti-cancer properties of natural products. Natural extracts can be tested by using preclinical animal models to check their efficacy. Many drugs are first tested in animals before going for a human trial. The efficacy of celecoxib was tested in a UV-induced skin cancer model before a human phase II trial. Aspirin and calcium results in colon cancer animal models were correlated with human data. The animal models can also determine potential pharmacodynamics markers for clinical trials. Animals models can help to understand the etiology and progression of the human cancer process and animal efficacy data remain central to the clinical trial decision-making process [62]

Cell lines derived from cancer cells are basic tools for cancer research and drug discovery. they act as a model to understand cancer and discover treatments for cancer as they retain most of the genetic properties of the cancer of origin. Animal models of cancer can help to understand both genetic and environmental elements responsible for the disease. The DMBA (7,12-Dimethylbenz(a)anthracene)-induced cancer in female rodents have become the typical laboratory model of mammary carcinogenesis [63]. DMBA-mediated biochemical, molecular, genetic, and histopathological changes in animals are in the same manner as found in human

cancers [64]. Diethylnitrosamine is used to induce liver cancer in animal models [65]. Benzo(a) pyrene is used to induce lung [66] and 1,2-dimethylhydrazine (DMH) and is induce colorectal cancer in animals used for cancer research [67]. Changes in genes in cancer are studied in s genetically engineered animal models [68]. These models represent the spontaneous development of cancer in its natural anatomical site and illustrate metastatic biology in the same manner as in humans. These models include transgenic and knockout mice [69]. Transplantable Tumor Models use cancer cell lines or tissues of humans to induce cancer in animals [70].

Conclusions

Natural products are the source of many clinically useful anticancer drugs. More than fifty percent of anticancer drugs have their origin from natural sources. Natural products with anticancer activity are reported in plants, microorganisms, and marine life which are almost sixty percent effective in cancer treatment.

Ethical approval

not applicable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation

but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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