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Plant-derived anticancer agents: A green anticancer approach

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ABSTRACT

Cancer is a frightful disease and represents one of the biggest health-care issues for the human race and demands a proactive strategy for cure. Plants are reservoirs for novel chemical entities and provide a promising line for research on cancer. Hitherto, being effective, chemotherapy is accompanied by certain unbearable side effects. Nevertheless, plants and plant derived products is a revolutionizing field as these are Simple, safer, eco-friendly, low-cost, fast, and less toxic as compared with conventional treatment methods. Phytochemicals are selective in their functions and acts specifically on tumor cells without affecting normal cells. Carcinogenesis is complex phenomena that involves many signaling cascades. Phytochemicals are considered suitable candidates for anticancer drug development due to their pleiotropic actions on target events with multiple manners. The research is in progress for developing potential candidates (those can block or slow down the growth of cancer cells without any side effects) from these phytochemicals. Many phytochemicals and their derived analogs have been identified as potential candidates for anticancer therapy. Effort has been made through this comprehensive review to highlight the recent developments and milestones achieved in cancer therapies using phytomolecules with their mechanism of action on nuclear and cellular factors. Furthermore, drugs for cancer treatment and their limitations have also been discussed.

1. Cancer: a global menace

Cancer is a severe metabolic syndrome and is one of the leading cause of death regardless of developments in the tools of disease diagnosis, treatment and prevention measures [1–3]. Cancer is one of the principal causes of mortality and morbidity around the globe and the number of cases are constantly increasing estimated to be 21 million by 2030 [4,5]. It is estimated that in 2017, the United States alone will have approximately 1688780 new cancer diagnoses cases and 600920 cancer deaths [6]. This uncontrolled proliferation of a normal cell which produces genetic instabilities and alterations

accumulates within cells and tissues which transforms normal cell into a malignant cell. These genetic instabilities include mutations in DNA repair genes (*p21*, *p22*, *p27*, *p51*, *p53* and tool box for DNA), tumor suppressor genes (*p53*, *NF1*, *NF2*, *RB* and biological breaks), oncogenes [*MYC*, *RAF*, *Bcl-2*, *RAS* (biological accelerators)] and genes involve in cell growth metabolism. Both external factors (radiations, smoking, tobacco, pollutants in drinking water, food, air, chemicals, certain metals and infectious agents) and internal factors (genetic mutations, body immune system and hormonal disorders) can cause cancer [7]. There are several types of cancer in human being; among these the lung cancer is reported the top listed in male followed by breast cancer in female [8,9]. Detailed information about several forms of cancer is given in Table 1. It is a major public health burden in both developing and developed countries being treated by medicinal plants as a whole or by their phytochemicals very frequently [10,11].

Previously, around 10.9 million new cancer cases, 24.6 million persons living with cancer, 6.7 million deaths reported

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around the world each year [12]. Based on World Health Organization (WHO) data, above 14.1 million new cancer cases and 8.2 million deaths were mentioned globally in the year 2012 and over 70% new cancer cases has been estimated during the next twenty years [13–15]. Nearly, 80% of the world's population depend on traditional medicines and more than 60% of clinically approved anticancer drugs are derivatives of these medicinal plant [16,17]. According to literature survey, there are many anticancer drugs clinically approved and are recommended for the cancer treatment [18,19].

Among these different forms of cancer, lung cancer is reported the most in male followed by breast cancer in female. The information is gathered from the cancer stat facts (<https://seer.cancer.gov/statfacts/more.html>) and cancer statistics (2017) by Siegel.

2. Drugs for cancer treatment and their limitations

A large number of efforts have been made to minimize the harmful side effects of drugs during the process of cancer therapy like preventing the side effects on the nearby cells and tissues, increasing drug accumulation and efficacy in the lesion, developing novel drug delivery and targeting systems [20]. There are so many other methods for the treatment of cancer like they involve surgery of tumor, radiotherapy, immunotherapy, chemotherapy, cancer vaccinations, photodynamic therapy, stem cell transformation or combination thereof often accompanied by severe side effects. Such side effects include limited bioavailability, toxicity, nonspecificity, fast clearance and restriction in metastasis [21,22]. Treatment methods depend

upon the cancer type, stage and location. Chemotherapeutic agents involve cytostatic and cytotoxic drugs which have shown promising results alone or in combination with other cancer therapies. These chemotherapeutic agents involve topoisomerase inhibitors [e.g. irinotecan (side effects include: neutropenia, sensory neuropathy, and diarrhoea) and doxorubicin (side effects include: cardiotoxicity), alkylating agents [e.g. oxaliplatin, melphalan, carboplatin, cisplatin and cyclophosphamide (side effects include: nephrotoxicity, gastrointestinal toxicity, cardiovascular toxicity, pulmonary and hematologic toxicity)], microtubules acting agent (e.g. vincristine, vinblastine, docetaxel and paclitaxel etc.) [18,23]. The above mentioned drugs are highly effective against a wide range of cancers, but these drugs are also having some limitations (side effects, expensive, very complex, not eco-friendly and toxic). There are cells in our body which multiply rapidly under normal physiological conditions like hair follicle cells, bone marrow cells and digestive tract cells etc., These present anticancer drugs also target these rapidly dividing normal cells which is a big challenge thus, harmful side effects arise. Due to these side effects there is decreased blood production, GIT inflammation, hair loss, immunosuppression, heart diseases and nervous disorders may arise. Another limitation is that these cancer cells resist to these drugs as they go through mutations. e.g., Drug resistant genes (ABCA4 and ABCA12) were over-expressed in human MCF-7 breast cancer cells respectively when docetaxel was applied. However, when phytochemical curcumin was applied in association with docetaxel down regulation of drug resistance genes was observed [24]. Thus, treating cancer cells by employing mono-target chemical agent is not an effective method. Therefore, based on extensive research findings, phytochemicals and their derived analogues possess most promising option for the better and less toxic cancer treatment [19].

Table 1

Organ based different forms of cancers and estimated new cancer cases and deaths by 2017.

S.No.	Cancer type	Estimated new cases in 2017	Estimated deaths in 2017
1	Bladder cancer	79030	16870
2	Lung cancer	222500	155870
3	Larynx cancer	13360	3660
4	Non-Hodgkin lymphoma	72240	20140
5	Oral cavity cancer	49670	9700
6	Liver cancer	40710	28920
7	Cervical cancer	12820	4210
8	Kidney cancer	63990	14400
9	Ovary cancer	22440	14080
10	Endometrial cancer	61380	19920
11	Colon and rectum cancer	135430	50260
12	Anal cancer	8200	1100
13	Brain & nervous system cancer	23800	16700
14	Testis cancer	8850	410
15	Melanoma (Skin)	87110	9730
16	Testis cancer	8850	410
17	Leukemia	62130	25500
18	Stomach cancer	28000	10960
19	Prostate cancer	161360	26730
20	Bone and joint	3260	1550
21	Breast cancer	252710	40610
22	Oral cavity & pharynx	49670	9700
23	Thyroid cancer	56870	2010
24	Pancreas cancer	53670	43090
25	Small intestine	10190	1390
26	Hodgkin lymphoma	8260	1070
27	Esophagus cancer	16940	15690
28	Myeloma	30280	12590

3. Current cancer therapy via phytochemicals: a novel approach

Medicinal plants serve as nature's gift to humans to help them pursue better health. Plants and their bioactive compounds are in medicinal practices since ancient times. Several medicinal plant species and their phytochemicals inhibit the progression and development of cancer [24]. It has been researched that plant kingdom comprised of approximately 250 000 plant species and only around 10% have been studied for treatment of different diseases. Phytochemicals and their derived analogues are present in different parts of the plant, e.g., flower, flower stigmas, pericarp, sprouts, fruits, seeds, roots, rhizomes, stem, leaf, embryo, bark and perform several pharmacological functions. Several plant products such as alkaloids, flavonoids, lignans, saponins, terpenes, taxanes, vitamins, minerals, glycosides, gums, oils, biomolecules and other primary and secondary metabolites play significant roles in either inhibiting cancer cell activating proteins, enzymes and signaling pathways [Cdc2, CDK2 and CDK4 kinases, topoisomerase enzyme, cycloxygenase and COX-2 (Cycloxygenase), Bcl-2, cytokines, PI3K, Akt, MAPK/ERK, MMP, TNK, mechanistic target of rapamycin (mTOR) (detailed information in Figure 1)] or by activating DNA repair mechanism (*p21*, *p27*, *p51*, *p53* genes and their protein products), Bax, Bid, Bak proteins, stimulating the formation of protective enzymes (Caspase-3, 7, 8, 9, 10, 12), inducing antioxidant action (antioxidant enzymes

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