Natural Products Chemistry & Research
ISSN: 2329-6836

Tesfaye and Ravichadran, Nat Prod Chem Res
2018, 6:4
DOI: 10.4172/2329-6836.1000330

Review Article Open Access

A Review on Anticancer Activity of Some Plant-Derived Compounds and Their Mode of Action

Tamrat Tesfaye* **and Yesudass Dominic Ravichadran**

Department of Chemistry, College of Natural and Computational Science, Wollega University, Nekemte, Ethiopia

***Corresponding author:** Tesfaye T, Department of Chemistry, College of Natural and Computational Science, Wollega University, Nekemte, Ethiopia, Tel: 251911862871; E-mail: tamrattesfaye2641@gmail.com

Received: June 15, 2018; **Accepted:** June 20, 2018; **Published:** June 26, 2018

Abstract

Cancer is a set of malignancies that has in common the aggravated and uncontrolled cellular growth, as well as the capacity of cellular invasion to different organs of the primary site. The ability of cancer cells to evade homeostasis and proliferate uncontrollably while avoiding programmed cell death/apoptosis is acquired through mutations to key signaling molecules, which regulate pathways involved in cell proliferation and survival. Compounds of plant origin, including food components, have attracted scientific attention for use as agents for cancer prevention and treatment. Many pharmaceutical agents have been discovered by screening natural products from plants. The exploration into natural products offers great opportunity to evaluate new chemical classes of anticancer agents as well as study novel and potentially relevant mechanisms of action. The mechanisms of action of plant-derived anticancer drugs possibly activate macrophages, induce apoptosis, and prevent oxidative damage of DNA, thereby controlling carcinogenesis that may be intrinsic or extrinsic. The present review summarizes the works so far conducted on this aspect with a view to provide a baseline information for promoting the plant-derived anticancer research in the present context of increasing cancer incidence, deprived of the cheaper, safer, and potent medicines to challenge the dreadful human disease.

Keywords: Cancer; Anticancer drugs; Phytochemicals; Pharmaceutical agents

Introduction

Cancer is a group of diseases where the cells grow abnormally and multiply through uncontrolled cell division. Cancer cells are more metabolically active than normal cells. It gradually invades and destroys nearby normal cells by forming a lump called a tumour. This is true of all cancers except leukaemia (cancer of the blood) [1-3]. Not all tumors or lumps are cancerous; benign tumors are not cancer. It is localized and of small size that tends to grow quite slowly. It does not spread to other parts of the body and is rarely life threatening. It is non invasive and unable to metastasize. On the other hand, malignant tumors are growing at high rate of division and have the ability to spread and destroy nearby tissues. Cells of malignant tumours can break off from the origin (primary) tumour and circulates through blood to other tissues which is called metastasis. Upon invading healthy tissue at the new site, it continues to divide and grow [4]. Both external and internal factors such as dietary fat intake, solvent and pesticide exposure, exposure to ionizing radiation (causing acute leukemias, thyroid cancer, breast cancer, lung cancer and others), smoking cigarette [5,6], some virus (HIV, HPV and Hepatitis B virus) and unhealthy lifestyle (being overweight, limited physical exercise, too much alcohol, too much sugar and red meat, not enough vegetables and fruit) can cause cancer [7-9]. Reactive oxygen species (ROS) refer to a group of oxygen-containing molecules that include superoxide radical anions ($O2^{\cdot-}$), peroxides, and hydroxyl radical ($OH^{\cdot}$) are free radicals which is one of the cancer causing agents by destroying a protein, an enzyme or even a complete cell. Once it is formed, it continuously propagates through chain reaction mechanism resulting in the release of thousands of the cellular oxidants that damage DNA (Figure 1) [7,10]. Of the existing human cancers, men are predominately affected by lung [11] and bronchus, prostate, colon and rectum, and urinary bladder cancer while women are more affected by breast, lung and bronchus, colon and rectum, uterine corpus and thyroid cancer. Now a day, many children are seriously affected by blood cancer and cancers related to the brain and lymph nodes. Cancer, an ever increasing global problem is not a single disease, but it is more than 100 different diseases [12]. This variety is a major challenge for its specific diagnosis and efficient treatment with single chemotherapy. It is associated with genetic disorder which is the result of mutations of DNA and changes in the genes that control the way cells function. Once the DNA is affected, there are no normal control systems that prevent cell overgrowth and the invasion of other tissues in cancer cells. The accumulation of mutation leads to further development of cancer which promotes new characteristics, including changes in cell structure, decreased cell adhesion, production of new enzymes and finally lead to death by invading other tissues [13]. Targeting at this change is used for the development of anticancer therapeutics. Alteration of epigenetic processes which is involved in cell growth and duplication leads to form cancer. Targeting to reverse the altered epigenetic function is also another way of finding new lead anticancer drugs [8,14]. Thus, the medical needs for cancer remain one of the most investigation areas in scientific research. Several studies have been carried out to prevent and treat cancers and still it needs further study to get the appropriate medicine which cures everybody with minimum limitation.

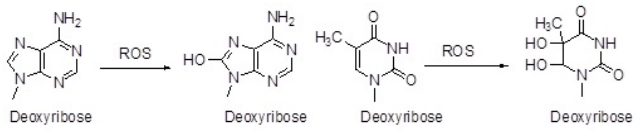


Figure 1: ROS oxidize DNA bases. The double bond of pyrimidines can be dihydroxylated and purines can be hydroxylated by ROS.

More than 3000 plant species have been reported as in use in the treatment of various cancer types [15]. There are infinite secondary metabolites in plant kingdom that responsible for protection against a variety of chronic ailments including cardiovascular diseases, obesity, diabetes, and cancer [1]. Flavonoids are among the most widely occurring phytochemicals having antioxidant property activate macrophage especially at site of infection and prevent carcinogenesis [16]. Now days, investigation on plant-derived drugs has got great attention over the world and search for anticancer drugs from plant is undergoing.

Drug discovery from natural products

Plants/herbs have been in use since ancient time as shelter, food and medicine. The medicinal properties of plants have been investigated in the recent scientific developments throughout the world and get attention due to their potent therapeutic efficacy, antioxidant activities, minimum side effects and economic viability. Plant derived natural products are nontoxic to normal cells and better tolerated hence they gain attention in modern drug discovery [17]. The therapeutic efficacy of plants depend on the availability of phytochemicals including alkaloids, flavonoids, polyphenols, saponins, terpenoids, steroids, glycosides, tannins, volatile oils and others. Plants/herbs have several compulsory pharmacological roles such as antioxidant, antiviral, anticancer, antimicrobial, antifungal and antiparasitic [17,18]. Over 60% of the currently used anticancer agents are derived from natural sources such as plants, marine organisms and microorganisms. The anticancer activity of most natural products often act via regulating immune function, inducing apoptosis, autophagy and inhibiting cell proliferation [19,20]. The possible way of discovering anticancer drugs from natural products involves testing of the crude extracts *in vitro* for its cytotoxicity on cancer cells without affecting normal cells, *in vivo* confirmation and clinical trial evaluation [8]. Once the crude extract is confirmed to have cytotoxicity toward cancer cell lines, fractionation of crude extract following test each fraction continued till the pure bioactive compound is discovered as anticancer drug.

Plant derived anticancer drug development process

Therapeutic efficacy of medicinal plants can be studied depending on certain factors like quality and quantity of the biological active of the phytochemical constituents, which vary with ecology of the soil, climate, and season and even vary from root to leave and age of the plant parts used for study. The new drug discovery and development process is a systematic approach to identify potential new drug candidates and their evaluation for drug-like properties. There are different approaches to purify bioactive compounds from the plant extracts. Acquisition of potential compounds is one of the important methods to achieve extraction from natural resources. This stage includes the development of analytical methods to confirm identity and purity of the compound, and its stability under real-life and stressed storage conditions. Drug discovery from medicinal plants has mainly relied on biological activity guided isolation methods which have led to the discovery of important drugs [21]. A preliminary screening in cell culture models or *in vitro* assays is carried out to identify the extent and specificity of its antitumor activity. The MTT(3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide)/MTS(3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) *in vitro* cell proliferation assay is one of the most widely used assays for evaluating preliminary anticancer activity of both synthetic derivatives and natural products and natural product extracts [11,22-25]. Once its bioactivity is known, screening continue with bioassay method to identify the potential therapeutic activity followed by further fractionation, isolation and structure elucidation of *in vitro*-active principles of initial lead bioactive supporting with various analytical techniques. This is followed by the evaluation of efficacy and toxicity in animal models [8,26,27].

Drugs for cancer treatment

Cancer treatment involves surgery, radiation and chemotherapy [5]. Surgery is the first line of therapy which is used to remove localized tumour at early stage of cancer. Radiotherapy is most often applied in a localized setting and conjunction with surgical procedures. The last one is chemotherapy (CTX), where in drugs are implemented with. This employs a wide group of drugs that have cytotoxic effects on cancer cells. Chemotherapy drugs are chemicals that can denature cancer cells by arresting their growth. The available anticancer drugs have distinct mechanisms of action which may vary in their effects on different types of normal and cancer cells. Since there are more than100 types of different cancers and have very few demonstrable biochemical differences between cancerous cells and normal cells, there is no single cure for cancer therapy. Though anticancer drugs affect dividing cancer cells, it is limited by their toxicity to normal cells of bone marrow, gonads (sex organs), gastrointestinal tract and skin (hair follicle cells). In addition to the aforementioned organs, liver and kidney (slow proliferating cells) are affected since they are the organs of metabolism or target organs of toxicity [28]. Therefore, cytotoxicity to normal cells challenged anticancer drugs discoverer to get drugs that selectively kill cancer cell without affecting normal cells.

The search for anti-cancer agents from plant started in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins [29]. According to biochemistry, mechanisms of anticancer action are: block nucleic acid biosynthesis, direct influence the structure and function of DNA, interfere transcription and block RNA synthesis, interfere protein synthesis and function and influence hormone homeostasis.

Plant-derived anticancer drugs in clinical use: Various classes of anti-cancer agents derived from plants are currently available for clinical use owing to their diverse mechanism of action. The approved plant-derived oncology cancer chemotherapeutic agents are vinca alkaloids, the epipodophyllotoxin lignans, the taxane diterpenoids and the camptothecin quinoline alkaloid derivatives. It was reported by different investigators that these classes of compounds have been found to act on two important biochemical targets tubulin and topoisomerase. Alkaloids (alkali-like) are basic nitrogenous plant products and generally contain a heterocyclic ring as their structural unit and show marked physiological actions. Alkaloids are mostly found in plants and also to some extent in microorganisms and even animals. Alkaloids are common in the angiosperms (mono and

dicotyledons), but rare in lower plants, although there are exceptions, for example pacletaxel from yew (a Gymnosperm). The vinca (*Catharanthus*) bisindole alkaloids vinblastine and vincristine (Figure 2) are the first significant anticancer alkaloids that have been in clinical use for the chemotherapy of a number of hematological and solid tumors for many years. The capacity of these alkaloids is to arrest cells in metaphase due to the fact that they inhibit the assembly and dynamics of microtubules. They are mitotic inhibitors, bind to microtubular protein 'tubulin' "vinca domain" site in the β-subunit, prevent its polymerization and assembly of microtubules, causes disruption of mitotic spindle and interfere with cytoskeletal function. The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine is a rapidly acting drug, very useful for inducing remission in childhood acute leukemia, but is not good for maintenance therapy. Other indications are lymphosarcoma, Hodgkin's disease, Wilm's tumour, Ewing's sarcoma and lung carcinoma. Even though it helps to kill cancer cells, its prominent adverse effects are peripheral neuropathy and alopecia. Bone marrow depression is minimal. Vinblastine is primarily employed with other drugs in Hodgkin's disease and testicular carcinoma. Bone marrow depression is more prominent while neurotoxicity and alopecia are less marked than with vincristine. Homoharringtonine is plant-derived alkaloid which shows anti-cancer properties by preventing protein synthesis. It has been widely used for the treatment of leukemia and myelodysplastic syndrome [13,30-36].

Podophyllotoxin (podofilox) and its derivatives, etoposide and teniposide, are all cytostatic (antimitotic) glucosides. The mechanism of action of podophyllotoxin lies in the formation of a complex with tubulin and prevention of the synthesis of microtubules. It blocks cell division in late S- and G2-phases of the cell cycle. It inhibits topoisomerase II, which results in DNA damage through strand breakage (Figure 3). It is useful against testicular and ovarian germ cell cancers, lymphomas and acute myelogenous and lymphoblastic leukemia [13,33,36-38].

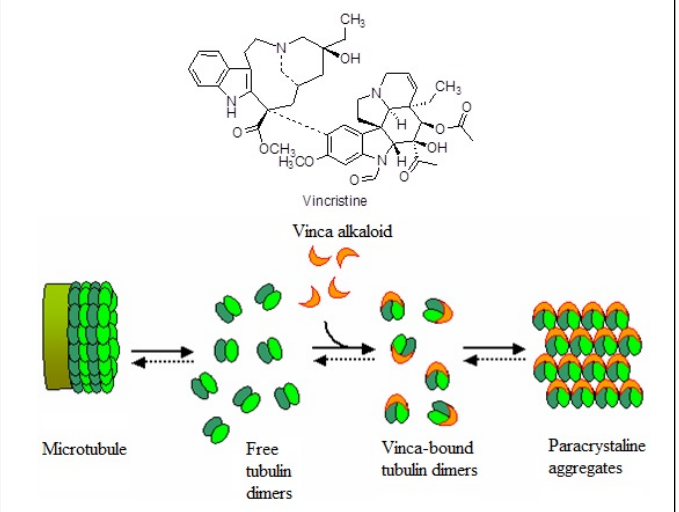


Figure 2: Mechanism of action of vinca alkaloid on microtubule.

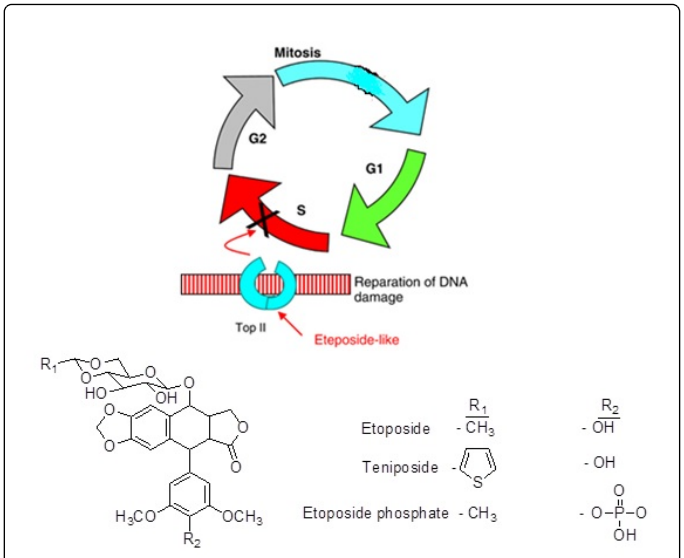


Figure 3: The mechanism of action of podophyllotoxin.

Paclitaxel and docetaxel are very important anti-cancer drugs that have exhibited some anti-cancer activity against several malignancies including metastatic breast and ovarian carcinoma, head and neck cancer, small cell lung cancer, oesophageal, adenocarcinoma and hormone refractory prostate cancer. The mechanism of action of paclitaxel is to bind to β-tubulin subunits of microtubules (Figure 4). It enhances polymerization of tubulin. The microtubules are stabilized and depolymerization is prevented which affect normal dyanamic reorganization of microtuble network that is essential for vital interphase and mitotic functions. Therefore, mitotic spindle poison [18,35,36,39-42].

This stabilizes the microtubule network, arrests the cell cycle at the G2/M phase, and therefore leads to apoptosis. Cancer cells have been found to evade the microtubule stabilizing action of paclitaxel through three main mechanisms: (1) over-expression of transmembrane efflux transporters, specifically effective antitumor activity and multidrug resistance protein; (2) tubulin mutations (both α and β) or alterations in the stability of the microtubule network; and (3) reduced function of significant apoptotic proteins [42].

Camptothecin (CPT) is plant derived drug that selectively inhibits topoisomerase I, thereby hindering DNA replication. Topotecan and irinotecan are derivatives of camptothecin, are used for the treatment of various types of cancers. They interact with Topoisomerase I (TOPI), a ubiquitous enzyme involved in the regulation of DNA topology during replication, recombination and transcription. TOPI forms a phosphotyrosine bond with DNA, catalyzing a forward reaction in which DNA is cleaved to allow unwinding, and a reverse reaction in which DNA is relegated. CPT interferes with the relegation step of this process by reversibly binding to and stabilizing the enzyme/DNA complex. A study performed with topotecan revealed that the CPT analog, acting as uncompetitive inhibitor, intercalated between the upstream (-1) and downstream (+1) base pairs at the DNA cleavage site. The intercalation resulted in a shift of base pairs and displacement of the 5'-OH strand away from the phosphotyrosine bond thus blocking relegation. This binding occurred whether E ring of topotecan was in the closed lactone form or the open carboxylate form (Figure 5); however, a higher occupancy rate (63%) was seen with

the lactone form. Further understanding of the interaction between the moieties on the CPT molecule and specific amino acids in the core of TOP1 may lead to appropriate modifications of the CPT rings to improve binding and cell kill. They arrest the cell cycle at the S-phase by inhibiting the activity of topoisomerase I, leading to the inhibition of DNA replication and transcription. Taxanes and camptothecins have been in clinical use and hold the large share in anticancer market [36,43,44].

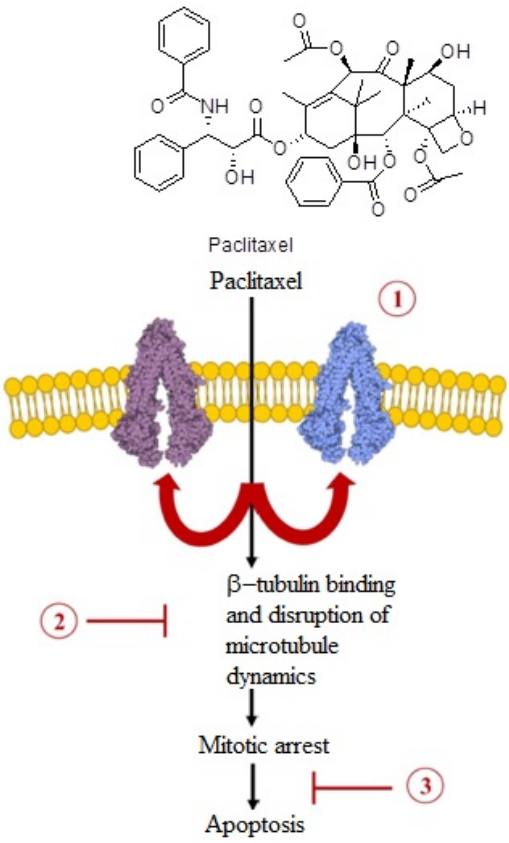


Figure 4: Paclitaxel enters the cell and binds to β-tubulin on the inner surface of microtubules.

Flavopiridol is one of flavonoid phytochemical constituent that acts by blocking cell division and induction of apoptosis. Some of its anti-tumor properties include inhibition of cyclins and Cyclin Dependant Kinases (CDK), induction of apoptosis and inhibition of angiogenesis. Combretastatins is effective against cancers of colon, lung and blood and also showed significant anti-angiogenic property. Betulinic acid possesses anticancer properties while silvestrol is effective against lung and breast cancer. Phytochemicals of flavonoids class are known for their anticancer properties. (-)-Epigallocatechin-3-gallate is known to prevent growth of malignant cells by modulating various cellular signaling pathways and inducing apoptosis of cancer cells selectively without affecting normal cells [13,36,38].

It was studied that the antiproliferative and cytotoxic activities of phenolic compounds depend on the number of OH-ring substituents. As OH-ring substituents increase, its antiproliferative and cytotoxic activities also increase. 3,4-Dihydroxyphenylethanoic acid and 3-(3,4-dihydroxyphenyl) propanoic acid hardly showed any cytotoxic activity toward mammary gland adenocarcinomas cell line. Trihydroxylated phenols showed significant cytotoxic effect toward lymphoblastic leukemia cell line. This may be partly due to the increased antioxidant ability of the unsaturated phenols, which seems to be associated with a protective effect of the cell integrity [23].

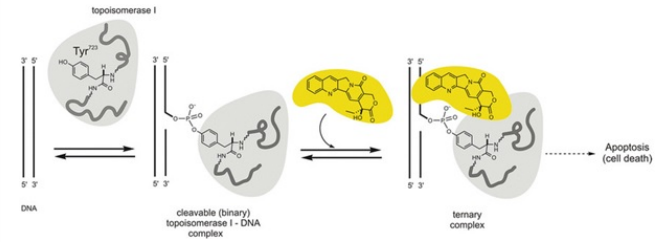
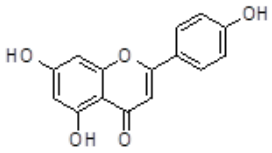
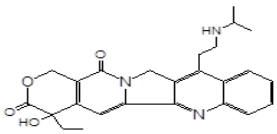
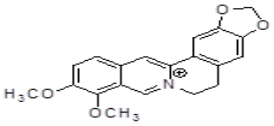
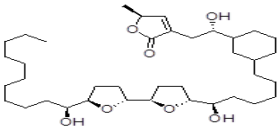
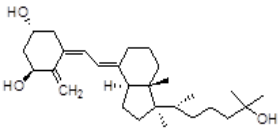
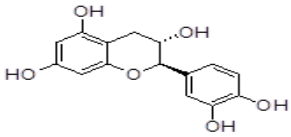
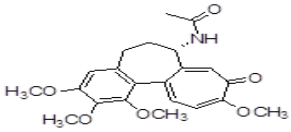
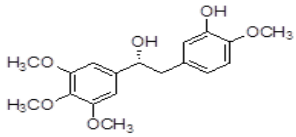
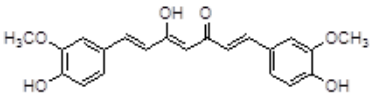
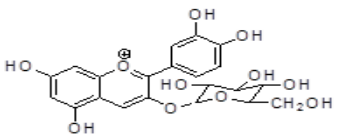
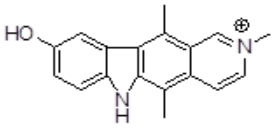


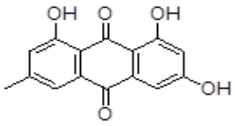
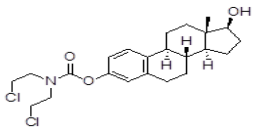
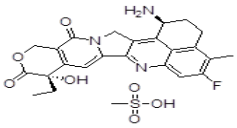
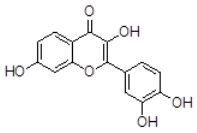
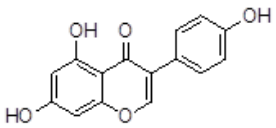
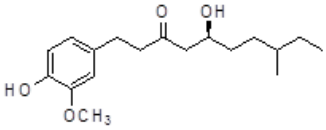
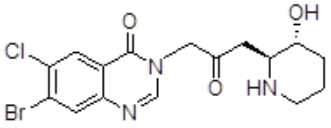
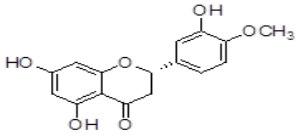
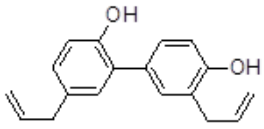
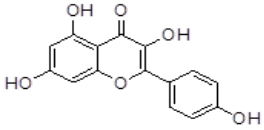
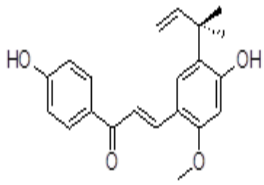
Figure 5: Mechanism of action of camptothecin.

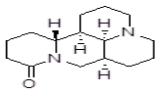
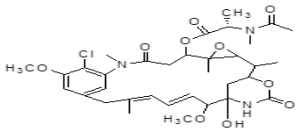
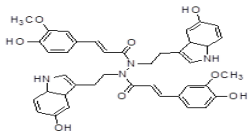
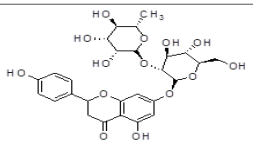
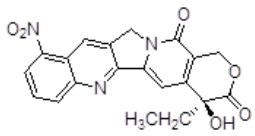
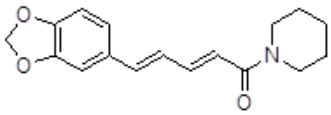
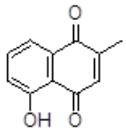
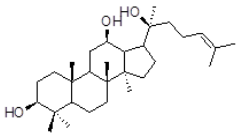
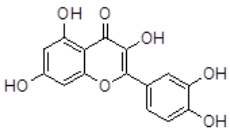
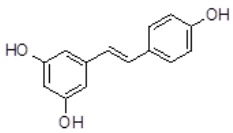
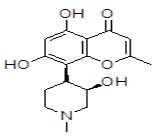
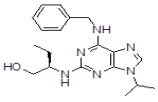
Antitumor antibiotics and topoisomerase inhibitors are obtained from plant derived natural products. The important inhibitors are camptothecin, irinotecan, topotecan for topoisomerase I and etoposide, teniposide, ellipticine etc., for topoisomerase II. These drugs inhibit the ability of the topoisomerase to cleave nucleic acid molecules. Although these types of drugs have important clinical efficacy, they have undesired and/or adverse effect such as drug resistance, poor bioavailability problems and myelosuppression. Furthermore, some of them lead to disruption or stabilization of DNA, so that these are also called as topoisomerase poisons. The other inhibitors of topoisomerase bind to enzyme or DNA and interrupt the catalytic activity of the enzyme and prevent the enzyme binding actions. In addition, a camptothecin derivative with a benzoxazole ring is shown significantly more potent than camptothecin as an inhibitor of DNA Topo I. It is of the opinion that a fused ring system in the chemical structure is critical and important for the biological activity [35,36,39,45,46].

Antibiotics which are used in chemotherapy have various modes of actions. Some are potent intercalating agents whereas some are DNA damagers. Some novel fused heterocyclic compounds like etoposide displayed more potent inhibitory activities. Molecular modeling of the possible structural motifs of the fused heterocyclic compounds, have been studied to expose their binding mode to eukaryotic DNA topoisomerase II by molecular docking studies. The interactions involved in the anti-tumour activities of fused heterocyclic compounds lead to the rational design of novel eukaryotic DNA topoisomerase II-targeted drugs [36,47,48]. There are also some plant-derived anticancer drugs in clinical use, clinical trials and pre-clinical trials to prove their efficacy as potent anti-tumor agents as mentioned in the Table 1 below.

Plant-derived anticancer compounds	Structure of compounds	Types of cancer treated	Status

Apigenin		Pancreatic cancer [8,39]	Preclinical trail
Belotecan		Ovarian, small-cell lung, and refractory colorectal cancers [13]	Clinical trials
Berberine		Tumorigenic micro-organisms and virus [32]	Preclinical trail
Bullatacin		Human ovarian tumor cells [49]	Preclinical trail
Calcitriol		Angiogenesis of cancer cells [8]	Preclinical trail
Cathechin and Epicatechin		MCF7 (human breast cancer cell line) [8,50]	Preclinical trail
Colchicine		Hepatocellular carcinoma cells, cholangiocarcinoma cells and Gastric cancer [32,38]	Preclinical trail
Combretastatin		Ovarian, colon, lung, gastric, other solid tumors, blood and anaplastic thyroid Cancer [13,36,50,51]	Phase-II trial
Curcumin		Melanoma cancers, Liver cancer cell lineHepG2), Leukemic monocyte lymphoma cell line (U937), Brain cancer cells and brain derived neural stem cells, Lymphoid leukemia and skin cancer [8,13,14,17,26,27]	Phase I-III oncological clinical trials
Cyanidin glycosides		Breast and colon cancer cells [8]	Preclinical trail
Elliptinium		Human breast cancer cell line (MCF-7) [7,31,52]	Clinical use

Emodin		Human colon cancer cells [5]	Preclinical trail
Estramustine		Prostate cancer [13]	Clinical trials
Exatecan		Acute myelogenous leukemia [50]	Phase-II clinical trail
Fisetin		Human acute promyelocytic leukemia cell line(HL-60) [8]	Preclinical trail
Genistein		Cancers of breast, uterus, cervix, lung, stomach, colon, pancreas, liver, kidney, urinary bladder, prostate, testis, oral cavity, larynx, and thyroid [8,14,27]	Phase I-III oncological-clinical trials
Gingerol		Colon cancer cells [8]	Preclinical trail
Halofuginone		Glioma, wilms tumer, hepatocellular carcinoma, bladder, prostate and pancreatic cancer	Preclinical trail
		Progressive advanced solid tumors [19]	Clinical use
Hespertin		Colon, cervical and breast cancer [39]	Preclinical trail
Honokiol		Lung, colon, liver, breast and prostate cancer [19]	Preclinical trail
Kaempferol		Pancreatic cancer cells [8]	Preclinical trail
LicochalconeA		Gastric cancer [40]	Preclinical trail

Matrine		Breast, gastric, lung cancer [40]	Preclinical trail
Maytansine		Breast cancer [52]	Clinical use
Montamine		HT29 (colon adenocarcinoma cell line), H460 (non-small cell lung carcinoma cell line), RXF393 (renal cell carcinoma cell line), MCF7 (human breast cancer cell line), and OVCAR3 (epithelial ovarian cell line) [7,31]	Preclinical trail
Naringin		TGF-β1/Smad3 (pancreatic cancer cell line) [39]	Preclinical trail
9-Nitrocamptothecin		A549 (lung cancer cells line) [18,40]	Clinical use
Piperine		Multi-drug resistance cancer, B16F10 (melanoma cancer cells line) [8,39]	Preclinical trail
Plumbagin		Leukemia, myeloma, breast, prostate, ovarian, pancreatic, liver, cervical and skin cancer [19]	Preclinical trail
Protopanaxadiol		Cytotoxic against multidrug-resistant tumors [50]	Clinical use
Quercetin		Ovarian cancer cell line (OVCA433), human cervical cancer, prostate cancer, epidermal growth factor receptor-over expressing oral cancer, osteosarcoma [36,40]	Preclinical trail
Resveratrol		Colon cancer	Phase I/II clinical trials
		Neuroblastoma, myeloma, breast, prostate, pancreatic and lung cancer [19]	Preclinical trail
Rohutikine		Ovarian and breast cancer [7]	Clinical trail
(R)-Roscovitine		Non-small cell lung cancer [53]	Clinical trail

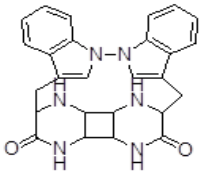
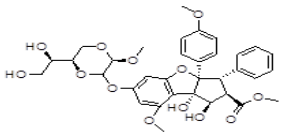
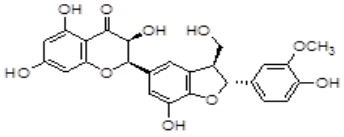
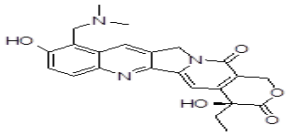
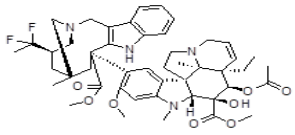
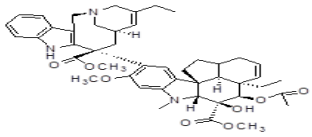
Schischkinnin		Colon cancer cell lines [7,31]	Preclinical trail
Silvestrol		Lung, colon, blood, prostate and breast cancer [13,50]	Clinical use Continued
Silymarin		Multi-drug resistance cancer [13]	Clinical use
Topotecan		Ovarian and small cell lung cancers, and colorectal cancers [39,52]	Phase II/III
Vinflunine		Metastatic transitional cell carcinoma of the urothelial tract [30,32]	Clinical use
Vinorelbine (Na-velbine)		Leukemia, lymphomas, advanced testicular, breast and lung cancer [32,37]	Clinical use

Table 1: List of some plant-derived anticancer drugs in clinical use and preclinical trails.

Conclusion

Increasing global warming, malnutrition, and various environmental risk factors are continued to increase the incidences of cancer. To decreases the problem relating with cancer, investigators have done many works to develop medicine. Despite remarkable progress in the discovery and development of novel cancer therapeutics, cancer remains the second leading cause of death in the world. Because, it is not a single disease, but it is more than 100 different diseases and associate with genetic disorder which is the result of mutations of DNA and changes in the genes that control the way cells function. So, natural product plant-derivatives play an important role to prevent the cancer incidences as synthetic drug formulations cause various harmful side effects to human beings. Plants are believed as one of the potential source of anticancer compounds, but they are least explored. Of the anticancer compounds isolated so far, the plants contribute only about 60%. Owing to a diverse chemical ecology, the plants/herbs have a great promise for providing potent, cheaper and safer anticancer drugs, which deserve an extensive investigation.

References

1. Kaur R, Singh J, Singh G, Kaur H (2011) Anticancer plants: a review. J Nat Prod Plant Resour 1: 131-136.
2. Chavan SS, Damale MG, Shamkuwar PB, Pawar DP (2013) Traditional medicinal plants for anticancer activity. Int J Curr Pharm Res 5: 50-54.
3. Jaikumar B, Jasmine R (2016) A Review on a few medicinal plants possessing anticancer activity against human breast cancer. International Journal of Pharm Tech Research 9: 333-365.
4. Nema R, Khare S, Jain P, Pradhan A, Gupta A, et al. (2013) Natural products potential and scope for modern cancer research. American Journal of Plant Sciences 4: 1270.
5. Agarwal N, Majee C, Chakraborthy GS (2012) Natural herbs as anticancer drugs. International Journal of Pharm Tech Research 4: 1142-1153.
6. Chanda S, Nagani K (2013) In vitro and in vivo methods for anticancer activity evaluation and some Indian medicinal plants possessing anticancer properties: an overview. Journal of Pharmacognosy and Phytochemistry.
7. Patel SG (2016) A Review on medicinal plants for cancer therapy. International Journal of MediPharm Research 2: 105-112.
8. Singh S, Sharma B, Kanwar SS, Kumar A (2016) Lead phytochemicals for anticancer drug development-A Review. Frontiers in Plant Science 7: 1-13.
9. Thomson AK, Heyworth JS, Girschik J, Slevin T, Saunders C, et al. (2014) Beliefs and perceptions about the causes of breast cancer: a case-control study. BMC Research Notes 7: 558.
10. Das R, Mehta DK, Chaudhary AK, Khan MU (2012) A review: Important herbs in treatment of cancer. International Journal of Research and Development in Pharmacy and Life Sciences 1: 135-142.

11. Paul S, Mandal SK, Bhattacharyya SS, Boujedaini N, Khuda-Bukhsh AR (2010) In vitro and in vivo studies demonstrate anticancer property of root extract of Polygala senega. Journal of Acupuncture and Meridian Studies 3: 188-196.
12. Shaikh R, Pund M, Dawane A, Iliyas S (2014) Evaluation of anticancer, antioxidant, and possible anti-inflammatory properties of selected medicinal plants used in Indian traditional medication. Journal of Traditional and Complementary Medicine 4: 253-257.
13. Biswas J, Roy M, Mukherjee A (2015) Anticancer drug development based on phytochemicals. J Drug Disc Develop Delivery 2: 1012.
14. Schneider-Stock R, Ghantous A, Bajbouj K, Saikali M, Darwiche N (2012) Epigenetic mechanisms of plant-derived anticancer drugs. Frontiers in Bioscience 17: 129-173.
15. Seca AM, Pinto DC (2018) Plant Secondary Metabolites as Anticancer Agents: Successes in Clinical Trials and Therapeutic Application. International Journal of Molecular Sciences 19: 263.
16. Rahman MA, Akhtar J (2017) Evaluation of anticancer activity of Cordia dichotoma leaves against a human prostate carcinoma cell line, PC3. Journal of Traditional and Complementary Medicine 7: 315-321.
17. Shakya AK (2016) Medicinal plants: future source of new drugs. International Journal of Herbal Medicine 4: 59-64.
18. Ramakrishnan R (2013) Potential clinical applications of natural products of medicinal plants as anticancer drugs–A Review. International Journal of Medicinal & Pharmaceutical Sciences 3: 127-138.
19. Juárez P (2014) Plant-derived anticancer agents: a promising treatment for bone metastasis. BoneKey Reports.
20. Rayan A, Raiyn J, Falah M (2017) Nature is the best source of anticancer drugs: Indexing natural products for their anticancer bioactivity. PloS One.
21. Lahlou M (2013) The success of natural products in drug discovery. Pharmacol Pharm 4: 17-31.
22. Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. Journal of Immunological Methods 65: 55-63.
23. Gomes CA, Girão da Cruz T, Andrade JL, Milhazes N, Borges F, et al. (2003) Anticancer activity of phenolic acids of natural or synthetic origin: a structure–activity study. Journal of Medicinal Chemistry 46: 5395-5401.
24. McCauley J, Zivanovic A, Skropeta D (2013) Bioassays for anticancer activities. In Metabolomics Tools for Natural Product Discovery. Humana Press, Totowa, NJ, pp: 191-205.
25. Kamil M, Jadiya P, Sheikh S, Haque E, Nazir A, et al. (2015) The chromone alkaloid, rohitukine, affords anti-cancer activity via modulating apoptosis pathways in A549 cell line and yeast mitogen activated protein kinase (MAPK) pathway. PloS One.
26. Fridlender M, Kapulnik Y, Koltai H (2015) Plant derived substances with anti-cancer activity: from folklore to practice. Frontiers in Plant Science.
27. Kinghorn AD, De Blanco EJC, Lucas DM, Rakotondraibe HL, Orjala J, et al. (2016) Discovery of anticancer agents of diverse natural origin. Anticancer Research 36: 5623-5637.
28. Rathod CP, Dhawale SC, Kshirsagar RV (2011) Recent trends in screening and evaluation methods of anticancer drugs. Indo American Journal of Pharmaceutical Research 1: 506-515.
29. Sisodiya PS (2013) Plant derived anticancer agents: A Review. International Journal of Research and Development in Pharmacy and Life Sciences 2: 293-308.
30. Ali R, Mirza Z, Ashraf GM, Kamal MA, Ansari SA, et al. (2012) New anticancer agents: recent developments in tumor therapy. Anticancer Research 32: 2999-3005.
31. Mohan M, Jeyachandran R, Deepa (2012) Alkaloids as anticancer agents. Annals of Phytomedicine 1: 46-53.
32. Coderch C, Morreale A, Gago F (2012) Tubulin-based structure-affinity relationships for antimitotic Vinca alkaloids. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 12: 219-225.
33. Poonam S, Chandana M (2015) A Review on Anticancer Natural Drugs. International Journal of PharmTech Research 8: 131-141.
34. Kumar S, Ahmad MK, Waseem M, Pandey AK (2015) Drug targets for cancer treatment: an overview. Med Chem 5: 115-23.
35. Crombag MR, Joerger M, Thürlimann B, Schellens JH, Beijnen JH, et al. (2016) Pharmacokinetics of selected anticancer drugs in elderly cancer patients: focus on breast cancer. Cancers 8: 6.
36. Li WW, Johnson-Ajinwo OR, Uche FI (2016) Advances of Plant-Derived Natural Products in Ovarian Cancer Therapy. International Journal of Cancer Research and Prevention 9: 81.
37. Creţu E, Trifan A, Vasincu A, Miron A (2012) Plant-derived anticancer agents-curcumin in cancer prevention and treatment. Rev Med Chir Soc Med Nat lasi 116: 1223-1229.
38. Nahata A (2017) Anticancer agents: a review of relevant information on important herbal drugs. Int J Clin Pharmacol Toxicol 6: 250-255.
39. Alam S, Satpathy P, Thosar A (2014) Plants and its parts as a source of anticancer compound: A review. Int Res J Pharm 5: 244-50.
40. Song Y, Sun H, Zhang A, Yan G, Han Y, et al. (2014) Plant-derived natural products as leads to anti-cancer drugs-A Review. Journal of Medicinal Plant and Herbal Therapy Research 2: 6-15.
41. Zhang S, MercadoUribe I, Liu J (2014) Tumor stroma and differentiated cancer cells can be originated directly from polyploid giant cancer cells induced by paclitaxel. International Journal of Cancer 134: 508-518.
42. Barbuti AM, Chen ZS (2015) Paclitaxel through the ages of anticancer therapy: exploring its role in chemoresistance and radiation therapy. Cancers 7: 2360-2371.
43. Legarza K, Yang LX (2006) New molecular mechanisms of action of camptothecin-type drugs. Anticancer Research 26: 3301-3305.
44. Pan L, Chai HB, Kinghorn AD (2012) Discovery of new anticancer agents from higher plants. Frontiers in Bioscience 4: 142.
45. Nagarani B, Debnath S, Kumar S, Bhattacharjee C, Kumar GG (2011) A review: Herbs used as anticancer agents. International Research Journal of Pharmacy 2: 20-24.
46. Alper S, Arpaci ÖT, Aki EŞ, Yalçin I (2003). Some new bi-and ter-benzimidazole derivatives as topoisomerase I inhibitors. Il Farmaco 58: 497-507.
47. Bhattacharya B, Mukherjee S (2015) Cancer therapy using antibiotics. Journal of Cancer Therapy 6: 849.
48. Tacar O, Sriamornsak P, Dass CR (2013) Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. Journal of Pharmacy and Pharmacology 65: 157-170.
49. Qayed WS, Aboraia AS, Abdel-Rahman HM, Youssef AF (2015) Annonaceous acetogenins as a new anticancer agent. Der Pharma Chemica, 7: 24-35.
50. Sharma S (2017) Review on Phytochemicals with their biological roles? - A Review. International Journal of Advanced Research in Biological Sciences 4: 69-77.
51. Prakash OM, Kumar A, Pawan Kumar A (2013) Anticancer Potential of Plants and Natural Products: A. American Journal of Pharmacological Sciences 1: 104-115.
52. Shoeb M (2006) Anti-cancer agents from medicinal plants. Bangladesh Journal of Pharmacology 1: 35-41.
53. Mariaule G, Belmont P (2014) Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules 19: 14366-14382.