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Advancement in Cancer Chemotherapy - An approach towards treatment with Traditional remedies

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ABSTRACT

Cancer is a global health problem responsible for one in twenty deaths worldwide. Advancement in cancer chemotherapy includes surgery and radiotherapy have been in use while significant advances are being made in recent times including stem cell therapy, natural antioxidants, targeted therapy, radionics, nanoparticles, chemodynamic therapy, sonodynamic therapy and ferroptosis based therapy. The search for effective treatment has gained much significance in the development of modern chemotherapy and the use of herbal medicines in the treatment of cancer. These approaches offer different perspectives on cancer treatment each with its own set of advantages and disadvantages. In this chapter, we explore the potential of modern chemotherapy and herbal remedies, exploring their differences, effectiveness, side effects, accessibility, and potential for consolidation in the treatment of cancer.

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Introduction

The term "chemotherapy" was coined by German chemist Paul Ehrlich which highlights the use of drugs to treat infectious diseases and multiplication of cancerous cells. The target of cancer chemotherapy is to limit unwanted growth of cell and tumor multiplication, thus avoiding metastasis and invasion. Prevention of cancerous cells can take place at different stages within the cell and its environment. Traditional chemotherapeutic agents primarily affect both function of neoplastic cells and macromolecular synthesis by blocking proteins synthesis or RNA, DNA affecting the related functions of the preformed molecule [1].

Conventionally Cancer treatment can be achieved by three incident in the last century Wilhelm Konrad Roentgen, who discovered "X-Ray" the use of transplantable animal-tumor models in cancer research, and the first surgical method developed by Halsted (radical mastectomy) [2]. Anthracyclines, mitomycin, and bleomycin etc are discovered anti-tumor antibiotics after the discovery of actinomycin D [3]. In 1947, Farber performed an experiment to treat childhood leukemia by using anti metabolites with antifolate activity called aminopterin later known as methotrexate [4]. The successful experiment performed of leukemias, choriocarcinoma and methotrexate led to further investigations in cancer chemotherapy and drugs like 5-fluorouracil, thiopurines (e.g., 6-mercaptopurine), came into the limelight of cancer treatment [5].

Many types of extended treatment protocols are available to treat the cancer which uses medication also called systemic therapies. These include

1. Chemotherapy
2. Hormone therapy
3. Targeted therapy
4. Immunotherapy

Different therapies can be used in a systemic way to treat cancer or a different drug or combination of drugs may be used to treat cancer. The type of long-term treatment depends on many different factors including the cancer type, location, stage, age, and the general health.

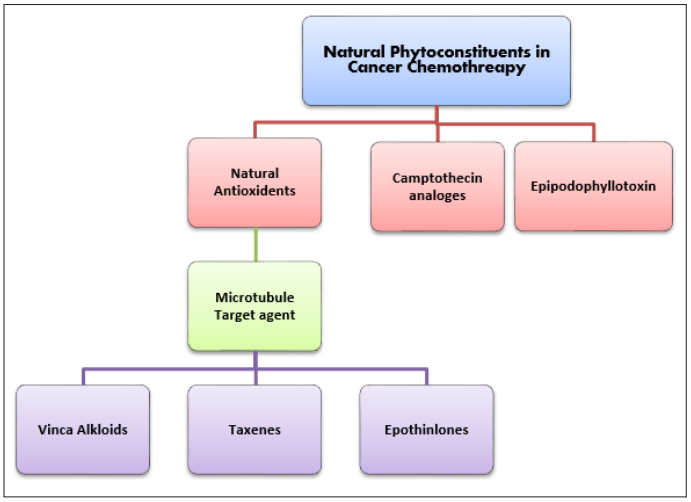
The treatment of cancer cells may stay the same over time which is in controlled state treatment may be stopped if the cancer is in remission and then restarted if it starts growing again.

It is also possible that the cancer cells can grow through cycles of growing and shrinking. If it continues to grow or spread, a different treatment may be recommended. In general, cancer treated in this way may change over time, but it does not go away completely [6].

Modern approaches in Cancer chemotherapy

In the recent survey it is stated that cancer has become a second major complication of human mortality rate, which significantly affects the human population. It is a constant demand to keep a search of new therapies which is required to treat and cure the cancerous cells. In recent times, herbal medicines have been drawn attention in many types of cancer treatment to overcome side effect. Traditional medicines from natural sources are been utilized for cancer treatment due to their potent anticancer effects. Plant secondary metabolites such as polyphenols, flavonoids, alkaloids and vitamins etc have potent anti-cancer properties and have been explored for cancer treatment for centuries. In scientific data base many studies have revealed that these secondary metabolites possess effective anticancer activities by exhibiting

several different mechanisms such as; apoptosis induction, target specificity, antioxidant activity prevention to DNA damage, angiogenesis prevention, cell cycle regression. Therefore, herbal plants and their bioactive compounds have emerged as a significant reservoir as various cancer chemotherapeutic agents.



Figures 1: Natural Phytoconstituents in Cancer chemotherapy

Traditional approaches in Cancer chemotherapy

Natural Anti-Oxidants

Polyphenols, Vitamins, alkaloids and plant-derived bioactive compounds are natural antioxidants used as preventive and therapeutic drugs against those molecules that damage the healthy cells due to their anti-inflammatory and antioxidant properties [7]. Many research works have addressed about cancer therapy after appreciating their proapoptotic and anti- proliferative properties. Compounds, such as carotenoids, quercetin, vitamins, alkaloids, flavonoids, curcumin, berberine, etc are examples of natural antioxidants that are examined in vitro and in vivo [8].

Bioavailability studies reveals that toxicity is major issues of natural drugs while their translation into clinical practice [9]. Curcumin has cytotoxic effects in different kinds of tumors like the brain, lung, leukemia, pancreatic, and hepatocellular carcinoma, while sparing normal cells at effective therapeutic doses [10]. The curcumin's biological properties, treatment duration and efficient therapeutic doses are under clinical practice [10]. Till date about 28 clinical trials are performed, while 45 are under analysis on curcumin.

Berberine is an alkaloid compound that has been studied to be effective against different cancers as a chemo preventive agent, modulating many signaling pathways. Different nano-technological strategies have been developed to facilitate its delivery across cell membranes due to their poorly soluble in water [11]. Seven clinical trials are under analysis and three have been completed.

Quercetin is effective alone and in combination with chemotherapeutic agents in treating many cancers, such as lung, prostate, liver, colon, and breast cancers [12]. Quercetin's mechanism of action is by binding to cellular receptors and the interference of several signaling pathways [13]. Currently, eight clinical trials are under analysis and six studies have been completed.

Microtubule-Target Agents

Microtubules are structures composed of α–β-tubulin heterodimers and microtubule-associated proteins representing one of the major components of the cytoskeleton. Microtubules are involved mainly in cellular processes including maintenance of cell structure, protein transportation and mitosis. They have central role of microtubules in mitosis drugs that affect microtubule are useful in cancer chemotherapy. Microtubule-Targeted Agents (MTAs) constitute a class of anticancer drugs largely used in the clinics to treat solid tumors and hematological malignancies, either alone or as part of different combination regimens. MTA are potent mitotic poisons that are broadly classified into microtubule-stabilizing (e.g. taxanes and epothilones) and microtubule-destabilizing (e.g. vinca alkaloids) drugs.

Vinca Alkaloids

They are the first natural anticancer agents approved to clinical use were the vinca alkaloids vincristine and vinblastine introduced in the late 1960s. Vinca alkaloids were isolated from the Madagascar periwinkle Catharanthus roseus and over thirty alkaloids have been obtained of which a few are known to be active [14]. There are three major vinca alkaloids in clinical use vinblastine, vincristine and vinorelbine. They are classified as destabilizing agents due to their ability to cause microtubule depolymerization, suppress treadmilling and dynamic instability, blocking mitotic progression, and ultimately result in cell death by apoptosis. Vinca alkaloids bind in one of three sites on tubulin, called the "vinca" domain, located near the exchangeable GTP binding site [15, 16].

Vinca alkaloids differ in their chemotherapeutic effectiveness being part of therapeutic schemes in different types of malignancies. Vincristine is used in combination chemotherapy for treating pediatric leukemias, Hodgkin and non-Hodgkin lymphoma, as well as solid tumors such as Wilms tumor and neuroblastoma [17, 18]. Vincristine can occasionally be used in the treatment of small cell lung cancer (SCLC). Currently, vinblastine is a standard component of regimens for treating lymphomas including Hodgkin's disease. It´s also used for the treatment of bladder cancer, testicular carcinomas, germ cell malignancies and breast cancer [19, 20]. Moreover, the semisynthetic derivate of vinblastine, vinorelbine, has activity against NSCLC and breast cancer [21, 22]. These compounds show severe neurotoxicity and observed less frequently with vinorelbine and vinblastine, this side effect is frequently noticed with vincristine [23, 24]. Myelosuppression, is associated with vinblastine and vinorelbine and is the main dose-limiting toxicity of those drugs [25].

Vinca alkaloids and the others MTAs can present resistance in cancer cells due to: (i) cellular efflux of the anticancer agents, especially by the over expression of drug efflux pumps, like multidrug resistance-associated protein 1 (MRP-1) and P-glycoprotein (ii) changes in micro-tubule-regulatory proteins (iii) changes in the tubulin isotype composition of microtubules (iv) Mutations in tubulin at the drug binding sites [26-30].

Taxanes

Taxanes are natural cytotoxic diterpene divide as microtubule-stabilizing anticancer agents. Paclitaxel and the semi synthetic analog docetaxel are considered to be among the most important anticancer drugs in cancer chemotherapy. Paclitaxel was identified in 1971 as part of a NCI program that screened medicinal plants for potential anticancer activity, whereof the researchers found cytotoxic effects on solid tumors and leukemic cells [31]. Paclitaxel was derived from the bark of the Pacific yew (Taxus

brevifolia) in a process that a centenary tree provides only a gram of the compound. This lead to a semi-synthetic method that use the 10-deacetylbaccatin-III, which is extracted from more abundant yew species such as the European yew Taxus baccata [32]. Docetaxel, in turn, is an esterified derivative of 10-deacetylbaccatin-III, produced by Potier and his colleagues in 1986 [33]. The structures of paclitaxel and docetaxel differ on the ester side chain attached at C-13 and in substitutions at the C-10 taxane ring position, which confers docetaxel slightly more water solubility than paclitaxel [34, 35]

These drugs interact with β-tubulin promoting tubulin polymerization and formation of stable microtubules, even in the absence of GTP- and microtubule-associated proteins, which are usually essential for these processes. This inhibition of microtubule depolymerization results in mitotic arrest leading to apoptosis of the cancer cells [36]. Furthermore, taxanes have been demonstrated to induce many other cellular effects that may or may not relate to their disruptive effects on microtubule dynamics, including the directly phosphorylation, hence inactivation, of proteins that blocks apoptosis in cancer cells (such as bcl-2) [37].

Paclitaxel was approved by FDA in 1992 for the treatment of refractory breast cancer and refractory ovarian cancer. Currently this agent has a central role in the treatment of breast, ovarian, NSCLC and AIDS-related Kaposi's sarcoma. In turn, docetaxel received the approval in 1995 for the treatment of metastatic breast cancer. Furthermore, was approved for use in hormone refractory prostate cancer (HRPC), advanced squamous cell carcinoma of the head and neck, breast cancer, gastric adenocarcinoma and NSCLC.

In order to overcome those problems, novel taxanes are in development as well as novel formulations. In 2005 Abraxane® (paclitaxel albumin-bound nanoparticles, solvent-free) was approved for advanced breast cancer. Abraxane® prevent the hypersensitivity reactions typically associated with paclitaxel, which are generally related to the solvent suspension of polyoxyethylated castor oil (Cremophor EL) [38, 39].

Taxanes exerts its primary toxic effects on the bone marrow, mainly neutropenia, and may cause neuropathy [40]. Docetaxel causes greater degrees of neutropenia than paclitaxel. Furthermore, docetaxel can cause fluid retention leading to peripheral edema and pulmonary edema, in extreme cases. Despite the high incidence of major hypersensitivity reactions due to the Cremophor EL vehicle, these reactions are no longer a serious problem due to the advent of effective premedication regimens and new formulations [41, 42].

Epothilones

Epothilones are new class of natural cytotoxic antineoplastic microtubule-stabilizing agents. Ixabepilone, a semisynthetic analog of the natural product epothilone B, is the only epothilone approved for cancer therapy, indicated for metastatic breast cancer. The epothilones competitively inhibit the binding of paclitaxel to polymerized tubulin, indicating that the two compounds share a common binding site despite significant structural differences [43]. It has been reported that ixabepilone is less susceptible to drug-resistance mechanisms that limit the efficacy of taxanes, like P-glycoprotein mediated efflux and the overexpression of class III β-tubulin, due to its reduction in polymerization rate of microtubules [44]. Likewise taxanes, ixabepilone is also formulated in Cremophor EL yielding hypersensitivity reactions. Other side effects related to its use are neuropathy, neutropenia, severe diarrhea and fatigue [45].

Camptothecin Analogs

Camptothecin was discovered as part of a NCI program in 1966 by Wall and Wani [46]. Camptothecin is a pentacyclic quinoline alkaloid present in wood, bark, and fruit of the Asian tree Camptotheca acuminate, that specifically target the topoisomerase I (Top-I), a nuclear enzyme that plays a critical role in DNA replication and transcription [47]. Top-I promote relaxation of the supercoiled DNA, prior to transcription, through the formation of a single strand break and religation. The camptothecins bind the covalent Top-I-DNA complex, known as the "cleavable complex", stabilizing it and inhibiting reannealing of the parent DNA. Consequently, camptothecins lead to reversible accumulation of double-stranded DNA breaks and tumor cell death [48].

Several derivatives of camptothecin have been synthesized but only irinotecan and topotecan have been approved for clinical use. Irinotecan and topotecan, which are more soluble and less toxic analogs, are currently used in a wide spectrum of cancers. Topotecan is part of regimens to treat ovarian, lung and cervical cancer. Irinotecan is a prodrug, currently used for metastatic colorectal cancer.

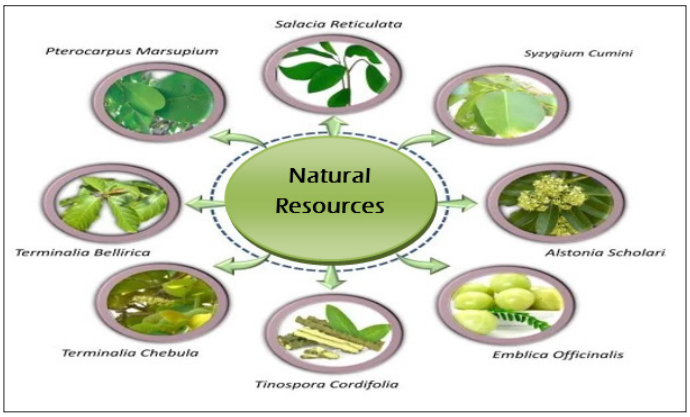
Irinotecan and topotecan produces dose-limiting side effects restricting safety administration and then their anti-tumor efficacy. Diarrhea is the principal side effect related to irinotecan. Moreover the use of this drug can cause nausea, vomiting, anorexia, fatigue, abdominal pain, alopecia and neutropenia. The principal toxicity of topotecan when administered at standard doses is neutropenia, while the nonhematological toxicities are usually mild [49, 50].

Epipodophyllotoxins

Podophyllotoxin was not used in clinical practice due to its toxicity while several less toxic compounds of Podophyllotoxin was discovered to treat lung and testicular cancer [51]. Some compounds such as etoposide and teniposide are significant in the treatment of childhood lymphomas and leukemias [52, 53].

They mainly act on topoisomerase II (Top-II). Top-II enzymes regulate essential cellular processes, including DNA replication and chromosome segregation. This types of enzymes induce transient double-stranded breaks in the DNA allowing DNA strands to pass through each other and unwind or unknot tangled DNA. Etoposide and teniposide inhibit Top-II to religate cleaved DNA molecules. The mechanism leads to accumulation of covalent complexes Top-II-DNA resulting in permanent DNA strand breaks which trigger mutagenic and cell death pathways [54].

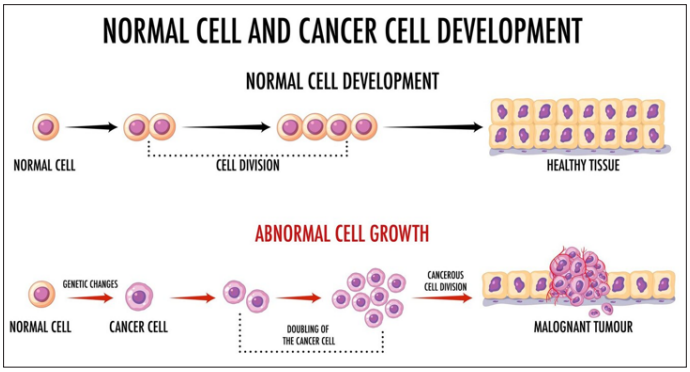
The agents lead to neoplastic transformation. Epipodo phyllotoxin therapy can cause AML characterized by chromosomal translocations, especially in chromosome [55, 56]. Most common side effects related to antineoplastic drugs might arise, such as bone marrow suppression, alopecia, nausea and vomiting.



Figures 2: Plant Drugs as Chemotherapeutic Agents

Future prospects - Linkage between Modern and traditional approaches in Cancer chemotherapy

Cancer treatment can be linked with various numbers of newer treatments which limits the multiplication of cancerous cells by stem cells, adult stem cells, cancer stem cells, pluripotent stem cells and traditional approaches. Stem cells are non-similar cells present in the bone marrow with an ability to differentiate into any type of body cell. Traditional medicines therapeutic strategy is one of the treatment options for cancer which are considered to be safe and effective. Scientific community extensively searching novel bioactive compounds from plants which shows remarkable therapeutic efficacy in the treatment of cancer. Researchers are in the attempted to verify and upgrade herbal medicinal products, their systematic survey, clinical trials and mechanism of action and bridging the modern scientific and traditional approach to combat cancer with newer phytomedicines and botanical drugs.



Figures 3: Normal Cell and Cancer Cell Development

Conclusion

In this review, we have attempt to explore the therapeutic potential of various novel bio active compounds from natural sources to combat cancer and to align the modern medicine with the traditional medicine in the treatment and prevention of cancer. A paradigm shift which integrates modern medicine and evidence based traditional medicine is inevitable. Therefore, educating patients and health care workers about traditional medicine use is imperative. This will enable health care workers to answer patient queries on traditional medicine use and guide their patients in seeking additional information for a particular therapy. Patients would ideally receive the maximum benefits from both modern medicine and traditional remedies.

Conflict of Interest

None

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